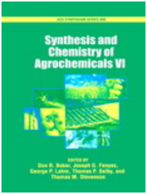

ACS SYMPOSIUM SERIES [illegible]

Synthesis and Chemistry of Agrochemicals VI

EDITED BY

Don R. Baker, Joseph G. Fenyes,
George P. Lahm, Thomas P. Selby, and
Thomas M. Stevenson

ACS SYMPOSIUM SERIES **800**

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Don R. Baker, Editor
Consultant

Joseph G. Fenyes, Editor
Buckman Laboratories International, Inc.

George P. Lahm, Editor
DuPont Agricultural Products

Thomas P. Selby, Editor
DuPont Agricultural Products

Thomas M. Stevenson, Editor
DuPont Agricultural Products

American Chemical Society, Washington, DC

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Foreword

The ACS Symposium Series was first published in 1974 to provide a mechanism for publishing symposia quickly in book form. The purpose of the series is to publish timely, comprehensive books developed from ACS sponsored symposia based on current scientific research. Occasionally, books are developed from symposia sponsored by other organizations when the topic is of keen interest to the chemistry audience.

Before agreeing to publish a book, the proposed table of contents is reviewed for appropriate and comprehensive coverage and for interest to the audience. Some papers may be excluded to better focus the book; others may be added to provide comprehensiveness. When appropriate, overview or introductory chapters are added. Drafts of chapters are peer-reviewed prior to final acceptance or rejection, and manuscripts are prepared in camera-ready format.

As a rule, only original research papers and original review papers are included in the volumes. Verbatim reproductions of previously published papers are not accepted.

ACS Books Department

Preface

Major changes in the synthesis and development of new agrochemicals has occurred in the past few years of the 20th century. Mergers and acquisitions within the industry have also changed the research environment. As we enter the 21st century, various agricultural biotechnological efforts are supplementing and replacing standard agrochemicals. However, the rise of biotechnology has not been without some controversy due to unresolved health concerns and political issues. Therefore, it is widely believed that traditional crop protection agents will play a major role in agriculture for some time to come.

The editors of these volumes have organized synthesis symposia at each American Chemical Society (ACS) national meeting since 1984. These symposia have been sponsored by the ACS Division of Agrochemicals with the aim of providing chemists with a forum for presenting the synthesis and chemistry of new agrochemical agents. The current book has chapters taken from the symposia presented at the Las Vegas ACS National Meeting held in the summer of 1997 through the Washington, DC ACS National Meeting held in the summer of 2000. Each of the chapter authors was requested to present the current status of the work at the time of preparation of the manuscript. In many cases considerably more effort has been done since the work was presented at the meeting. These chapters present a unique look into the discovery process of our current and future agrochemical products. Not all of the chapters represent materials that will eventually be commercialized. It is hoped that these chapters will also provide a learning experience both for those working in this field and for others interested in the biological effects of organic molecules.

As with the previous volumes, our goal is to inform the reader of the current trends in research for safe, efficient, biologically active agrochemicals. The organization of this book is similar to that of the preceding volumes. After the overview chapter, a section describes efforts in the discovery of new herbicides. The next section describes the discovery of new insecticides and highlights the discovery of and development of the new DuPont insecticide Indoxacarb. The final section deals with the control of plant fungal diseases.

Acknowledgments

We express our thanks to the authors and their employers who have shared with us the details of their interesting research results—first at the

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symposia and then in going that extra mile to prepare the chapters for publication. We hope that you our readers—whether you are our fellow synthesis chemists, or microbiologists, entomologists, plant physiologists, biotechnologists, as well as medicinal and pharmaceutical chemists—will find the chapters interesting, useful, and above all stimulating!

Last, but not least, we also wish to thank DuPont and Buckman Laboratories International, without their generous support of these symposia, this volume could not have been published.

Don R. Baker
Consultant
15 Muth Drive
Orinda, CA 94563
drbaker@home.com

Joseph G. Fenyes
Buckman Laboratories International, Inc.
1256 North McLean Boulevard
Memphis, TN 38108
jgfenyes@buckman.com

George P. Lahm
Stine-Haskell Research Center
DuPont Agricultural Products
Building 300, P.O. Box 30
Newark, DE 19714–0030
george.p.lahm@usa.dupont.com

Thomas P. Selby
Stine-Haskell Research Center
DuPont Crop Protection
Building 300, Room 126
P.O. Box 30
Newark, DE 19714–0030
thomas.p.selby@usa.dupont.com

Thomas M. Stevenson
Stine-Haskell Research Center
DuPont Agricultural Products
P.O. Box 30
Newark, DE 19714–0030
thomas.m.stevenson@usa.dupont.com

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Chapter 1

Synthesis of Agrochemicals and Agricultural Biotechnology in Modern Agriculture

Don R. Baker[1], Joseph G. Fenyes[2], George P. Lahm[3], Thomas P. Selby[3], and Thomas M. Stevenson[3]

[1]Consultant, 15 Muth Drive, Orinda, CA 94563
[2]Buckman Laboratories International, Inc., 1256 North McLean Boulevard, Memphis, TN 38108
[3]Stine-Haskell Research Center, DuPont Agricultural Products, P.O. Box 30, Newark, DE 19714

The process of finding and developing new crop protection products is evolving at a rapid pace. The emergence of biotechnology in agriculture represents a new frontier for our industry. Advances in communication, data acquisition, data storage and rapid exchange of information via the internet are reshaping the industry. The challenges of agriculture worldwide and how they relate to modern science are explored in various aspects of this book. An update on the global crop protection market, evolving research models, the influence of biotechnology and the future for crop protection chemicals are topics in this chapter.

Introduction

The demand for agricultural products continues to grow in the face of one of the toughest agricultural economies in decades. World population passed 6 billion in October 1999 and continues to increase at an annual rate of 1.3 percent, or yearly at 78 million people. Further, four fifths of the world population is in underdeveloped countries, where 98% of the population growth has taken place (1). The increase in demand for the world food supply sits in stark contrast to the depressed agrochemical industry and the plight of the farmer facing reduced export demands and record low crop prices. The agricultural industry is thus faced with the challenge of maintaining the quality of a global food supply in sufficient quantity to meet growth demands. This takes place in a difficult economy where ever-increasing demands are rightly placed on crop protection products to insure high margins of safety to people and the environment.

The industry has seen an evolution in the quality of crop protection products to meet these demands. Significant scientific breakthroughs have continued to uncover products which act at lower use rates, show high specificity for the target pest and are rapidly degraded in the environment. Increased demands by regulatory agencies, the ongoing development of resistance and the evolving nature of the industry will continue to fuel the need for new products.

But, today perhaps we sit at the threshold of what could be the most significant transformation the industry has seen since its inception, that is the impact of biotechnology. Herbicide resistant crops such as Round-Up Ready beans and insect resistant crops such as Bollgard cotton have emerged to take their place in the farmers arsenal of crop protection. In the future we imagine farmers will grow customized crops which will be tracked from seed to field to consumer. The impact of biotechnology is perhaps more than we can envision at present. There has also been significant global backlash, most visibly in Western Europe, as biotechnology continues to make inroads into the agricultural economy. As with the arguments against crop protection chemicals of the past, we can only assume that the antibiotech movement will continue to voice its concerns. It is incumbent on our industry to prove and defend the promise and benefits that biotech offers. And further, we must

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meet public concern with open dialogue, significant education, and sound evidence regarding safety and quality of world food, specifically regarding implications of biotechnology.

The Global Crop Protection Market

The entire global crop protection market for the year 2000 was estimated to be about $31 billion and is not expected to grow substantially over the next five years. Conventional crop protection chemicals represented the major part of this global market with agbiotechnology contributions growing, but at less than 10% of the total world value. Herbicides accounted for about 45%, insecticides 22% and fungicides almost 20% of worldwide sales. Along with fruits and vegetables, key crops in the world continue to be cereals, corn, soybeans, rice, cotton, oilseed rape and sugarbeets. Key regions in the world for traditional crop protection chemicals remain North America, Western Europe, East Asia and Latin America. Interestingly, North America is still the major market for biotechnology sales with Western Europe being second although far distant in sales (*2*).

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Due in part to the relatively static size of the global crop protection market we've seen a continued decline in the number of major agrochemical companies principally through mergers and acquisitions. Simultaneously, we have seen pharmaceutical companies exit the agrochemical business to concentrate on their more profitable pharmaceutical markets. At the top of the industry this has created several agrochemical companies with an excess of 10% global market share. The two largest of these being Syngenta (formed from the merger of Novartis and Zeneca) at 6.4 billion in 1999 annual sales (22% market share) and Aventis (formed from the merget of Rhone-Poulenc and AgrEvo) at 4.1 billion in 1999 annual sales (15% market share).

Top agrochemicals, with sales at or over a quarter billion dollars for the year 2000 were as follows: glyphosate, paraquat, acetochlor, atrazine, 2,4-D, metolachlor, pendimethalin and simazine (herbicides), chlorpyriphos and imidacloprid (insecticides) and azoxystrobin, mancozeb and tebuconazole (fungicides) (*3*).

Discovery of New Agrochemicals

The discovery of new and useful agrochemicals continues to rely heavily on the discovery of high quality leads. The many and varied ways for new lead discovery and their optimization toward commercial agrochemicals has been detailed in this series of ACS books (4-8). Lead sources have included natural products, pharmaceutical compounds and synthesis and acquistion of novel compounds. In the search for novel leads the trend has been toward increased screening capacity particularly through the use of large compound libraries. And, the future is progressing toward focused compound libraries that input desirable chemical and physical property traits.

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Historically, natural products have served as a rich lead source and have contributed significantly to many current commercial agrochemical products. The pyrethroids provide the most striking example with over 30 registered products. The evolution of structure-activity for synthetic pyrethroids provides striking evidence of the wide range of chemical opportunity that exists from a single lead source. Not only were dramatic rate improvements realized, (e.g. cyhalothrin, baythroid and bifenthrin), but fine attention to physical property and market requirements expanded pyrethroid utility into the soil (tefluthrin) and rice markets (ethofenprox).

It is perhaps instructive to look at some of the significant new products introduced in the marketplace over the last five years to get a picture of recent successful discovery strategies. Like pyrethroids, strobilurins have as their genesis leads from natural products. Strobilurins have become major players in the fungicide market with the leader, azoxystrobin (Syngenta, 1997), at annual sales at over 400 million in 2000. New strobilurin fungicides containing heterocyclic replacements for the methoxyacrylate are described in a chapter of this book, and demonstrate the evolving structure activity trends for this class. The lepidopteran insecticide spinosyn (Dow, 1997) was discovered through fermentation technology, followed by extensive screening and characterization. Several chapters in this book detail synthetic modifications to spinosyn and link fermentation and synthetic technology as a discovery strategy.

Imidacloprid (Bayer, 1991), a member of the neonicotinoid class of insecticides, and indoxacarb (DuPont, 2000), an oxadiazine insecticide share similar discovery histories. The leads for both were identified through random screening in the early 70's. Both classes of chemistry were successfully optimized to higher active materials over the following decade, although

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limitations in spectrum, rate and toxicological parameters prevented commercial utility. Efforts to understand the limitations and address these through optimization identified successful solutions in each case. Imidacloprid was introduced in 1991, with annual sales now in excess of 450 million and indoxacarb was introduced in 2000, and is now in its first full year of sales. The discovery of the newest neonicotinoid, thiamethoxam (Syngenta), is described in one of the chapters of this book. Several chapters are devoted to the discovery history of indoxacarb.

More recently combinatorial chemistry and high throughput biological screening have emerged as strategies for the discovery of new agrochemicals similar to that of the pharmaceutical industry. The goal has been to find compounds of promising biological activity that can be modified through second and third generation libraries or optimized by conventional synthetic methods to more advanced leads and products. Small combinatorial chemistry companies have surfaced to help fill the supply need for large libraries. At the same time agrochemical companies have invested significantly into in-house technology aimed at increasing combinatorial capability as a means for both discovery and optimization. Our lead chapter exemplifies the use of combinatorial chemistry in agrochemical discovery (*9*).

Finally, there has been a recent trend, in both the pharmaceutical and agrochemical industry, to leverage portions of research and development through strategic alliances with smaller service companies (10). The allows companies the flexibility to adjust to rapidly changing work demands and staffing needs to meet a variable workstream. As a result, the number of small contract research companies has grown substantially. These organizations now offer a wide array of services including custom synthesis, process development, chiral synthesis, cGMP (good manufacturing practices) capabilities, enzymatic work and consulting (*11*).

Biotechnology and Agriculture

In the biotechnology field, there has been enormous growth in both knowledge and application to agriculture. Soybeans were the first genetically modified crop. Engineered to be resistant to Roundup herbicide, Roundup Ready soybeans were launched by Monsanto in 1996. This has made the fastest inroad of any agricultural application. About 37 Million acres or 50% of the soybean crop were planted with Roundup Ready soybeans in 1999. Insect-resistant and other modified corn accounts for 25 million acres or 33% of the US's 1999 corn crop.

New agricultural biotechnology discoveries continue at a rapid pace. Rice has become the first major crop to have its entire genome determined. Syngenta, in collaboration with Myriad Genetics, recently completed the genetic map and is now analyzing rice gene expression and protein formation in rice (*12*). Monsanto has also recently announced that they have a rough draft of the rice genome. Both Syngenta and Monsanto have expressed a willingness to share their information with the academic research community through collaborative agreements. Farmers in the US and Canada now have more than 60 registered crop products approved by government agencies for use (*13*).

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The rise of agbiotechnology has not been without controversy (*14*). Europe has been slow to warm to biologically engineered food products, and, there has been a backlash against genetically modified crops. England, Germany and France appear most vocal in their opposition to such products. In 2000 a mix-up of bioengineered corn approved for use as animal feed but not for human consumption brought a nationwide recall of taco shells in the United States (*15, 16*). The event was considered a setback for the agbiotech industry and also heightened consumer concerns.

Due to these and other unresolved issues many agrochemical companies are reevaluating and modifying their efforts behind agbiotechnology. In some cases, new product introductions have been slowed or delayed. However, the benefits that agbiotechnology offers will most likely guarantee that new commercially viable products from this field will continue to be introduced into the marketplace. We are confident these new products will make significant and positive contributions to world agriculture.

Future of Crop Protection Chemicals

The National Research Council (NRC) has concluded in a recent report that synthetic chemical pesticides will continue to play a key role in U.S. agriculture for at least the next decade (*17*). The benefits of traditional crop protection agents are believed to be high relative to their risks. In some crops, biotechnology alternatives simply do not exist at this time. Time will also be needed for political and consumer health issues to be resolved before more widespread use of biotechnology can be adopted. Therefore, the NRC has advocated that chemical agents remain an essential part of integrated pest-management tactics. The crop industry agrees with this conclusion and the American Crop Protection Association has stated that growers continue to need a wide range of options available to them for crop protection (*17*).

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Chapter 2

Screening Mixtures: An Experiment in Pesticide Lead Generation

Karl J. Fisher[1,2], Ray A. Felix[1,2], and Robert M. Oliver[1,3]

[1]Zeneca Agrochemicals, 1200 South 47th Street, Richmond, CA 94804
[2]Current address: Cambridge Discovery Chemistry, 1391 South 47th Street, Richmond, CA 94804
[3]Current address: Pfizer Global Research and Development, Pfizer, Inc., Groton, CT 06340

The screening of mixtures[1-3] was evaluated as a way of improving the rate of new lead generation, one of the greatest challenges facing modern agricultural chemists. We have observed mixture hits on our herbicide screens; when we have deconvoluted these mixture hits by making all of the mixture components we have, in every case, observed activity from single compounds. In some cases, the activity is cumulative with activity found for more than one component of the mixture. In other cases, all of the activity comes from a single component of the mixture.

The discovery of new chemical classes with novel modes of action poses one of the most challenging problems faced by scientists doing agrichemical research[4-9]. One typically has to screen thousands of compounds to find a hit of sufficient activity and novelty to warrant follow up chemistry by an optimization

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team. In order to increase the number of compounds tested in our primary screens without increasing staff, we decided to make compounds as mixtures by reacting mixtures of alkyl halides with a variety of single nucleophiles. We chose to make mixtures of ten compounds rather than larger mixtures to simplify the identification of any active compounds: Ten halides (RX) + one nucleophile NuH forms ten products (10NuR) + HX, where X = halogen. Any active mixture would be deconvoluted by simply preparing the ten expected reaction products and screening them individually. The mixtures of ten alkyl halide regents were made up as equimolar reagents in acetonitrile (0.10M per component, 1.00M total) and heated with one equivalent of nucleophile, 1-1.5 equivalents of KI and 1.1 equivalents of base (usually sodium hydride or potassium t-butoxide). Prior to producing mixtures, candidate nucleophiles were checked for suitability by heating with 4-(4-methylphenoxy)-1-chlorobutane, an unactivated alkyl halide. Nucleophiles which did not react cleanly with this halide were not used to make mixtures. A typical mixture of alkyl halides is shown in Figure 1:

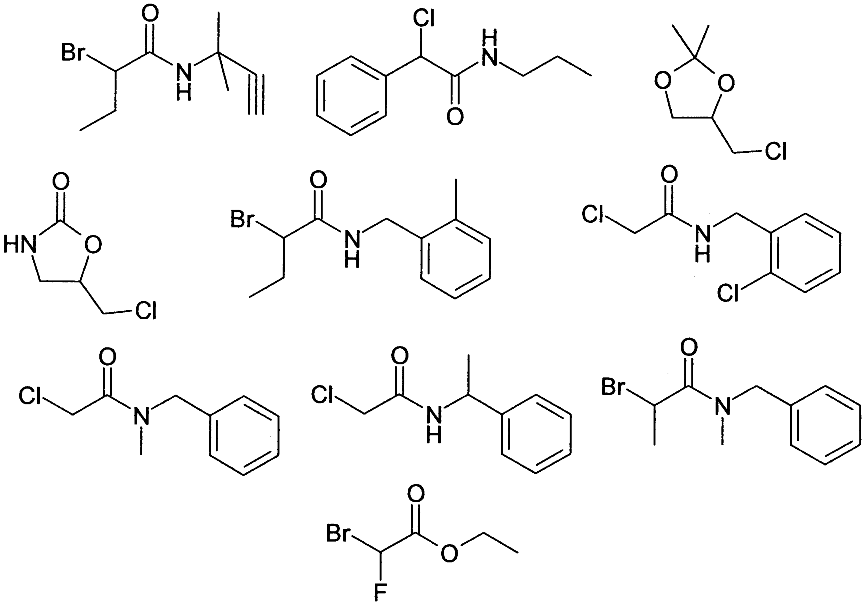

Figure 1: A typical mixture

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Synthetic Studies and Screening Strategy

Our initial studies focused on the alkylation of 4-substituted pyrazoles. We also alkylated other nucleophiles successfully including mercaptans, heterophenols, phenols, select alcohols, thioureas and imides. As a gereral guiding principal, we tried to incorporate at least three potential binding groups per molecule. Examples of binding groups are aromatic rings, carboxamides, esters, sulfonamides or heterocycles. We assumed that molecules with only two potential binding groups were too simple and, if active, were only too likely to have precedents in the literature. In the first year using the mixture strategy 700 mixtures (7000 compounds, theoretically) were prepared by one chemistry team of two people. We agreed on a screening rate of 10lb per acre, 1lb per component based on our knowledge that, historically, individual compounds were screened at rates up 20lb without getting too high a hit rate and modern screening rates are in the range of 1-4lb per acre. When components from hits were tested, they were tested at both a 1lb rate and at a 4lb rate. Without testing components at the 4lb rate, the activity of cumulative hits (hits where more than one component had activity) could never have been assigned to individual components. From 700 mixtures, thirteen types of herbicide hits were obtained. The first hit obtained was deconvoluted by preparing the components which were screened individually. Six of the components were inactive.

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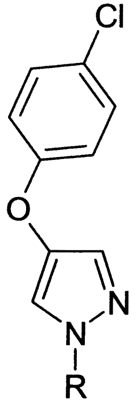

Figure 2: Reaction mixture 1, our first hit contained compounds **I-IV**

The active compounds **I-IV** from this mixture had the order of activity R=$-CH_2COOEt$ > $-(CH_2)_5COOEt$ > $CH(CH_3)COOEt$ > $(CH_2)_4COOEt$ and all four compounds had 2,4 D like symptomology. This type of auxin activity is frequently observed for both our mixtures and for intermediates submitted at random for herbicide screening.

The second active mixture we obtained was prepared by alkylating ethyl 2-mercapto-5-methyl-4-imidazolecarboxylate. When we tried to make the ten components only seven formed; upon screening these seven compounds we found that all of the activity came from a single component, compound **V**:

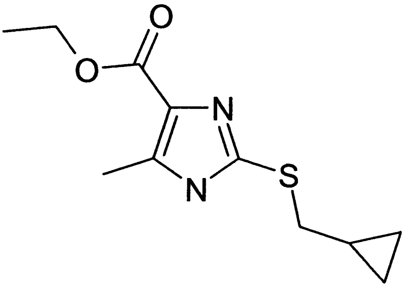

Figure 3: Compound **V**

Compound **V** had activity only on broadleaf weeds and, while interesting, was not active enough to encourage further synthesis. This compound had a rapid leaf burn effect similar to a PPGO herbicide[10,11] or PSII inhibitor[12-14]. We also got several hits which upon inspection were closely related to known series of herbicides which inhibit phytoene desaturase or were covered in previous patents.

We also found some herbicidal activity from two novel types of mercaptotriazoles. Compounds **VI** and **VII** were prepared by alkylating the appropriate mercaptotriazole with commercially available benzyl chlorides:

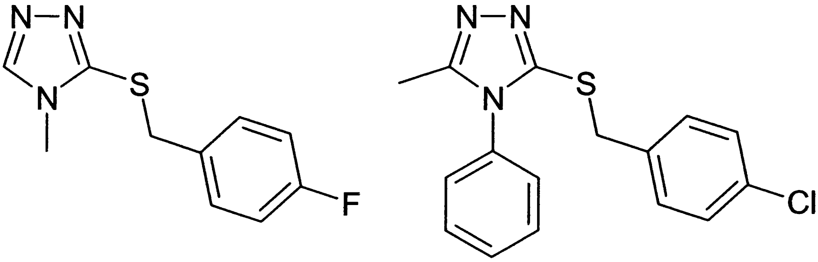

Figure 4: Compounds **VI** and **VII**

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Both of these compounds were present in mixtures which had cumulative activity. The N-methyl triazole compound **VI** had preemergence activity on some grasses with a rapid leaf burn effect. The N-phenyl triazole compound **VII** caused a bleaching effect similar to phytoene desaturase inhibitors. However, it was not active when tested in this assay[15].

The most interesting herbicide we found is this previously unknown triazolylthioacetamide, compound **VIII**:

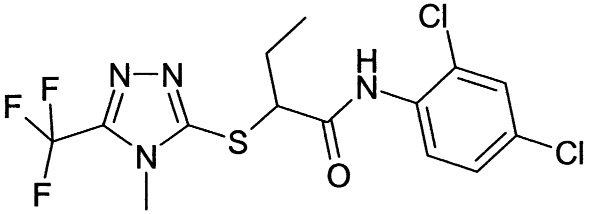

Figure 5: Compound **VIII**

This compound was prepared by alkylating the mercaptotriazole with N-(2,4-dichlorophenyl) 2-bromoisobutyramide. None of the other components of this mixture had any activity. This compound controls both grasses and broadleaf weeds at 1 pound per acre and controls some of the more susceptible weeds at a quarter pound per acre. As far as we were able to determine this compound has a new mode of action. Since this compound has significant activity and is reasonably easy to prepare, it became a starting point for a lead optimization effort.

Conclusions

Without any laboratory automation, we were able to prepare large numbers of compounds and identify some new herbicidally active chemicals reasonably quickly using our mixture strategy. Screening mixtures can be an effective strategy, particularly when screening capacity is limited and false positives are rare.

Acknowledgments

We would like to thank Derek Dagarin, Nick Polge, Sean Hanser and Chris Knudsen, our good friends in Weed Science, for testing all of these mixtures and accommodating all of our requests. Without their spirited efforts this work would never have been accomplished.

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Chapter 3

Synthesis and Structure–Activity Relationships in a Novel Class of *N*-Aryl Lactam Herbicides

Glynn Mitchell, Nigel J. Barnes, John M. Cox, Ian R. Matthews, David R. Parry, David P. J. Pearson, and Stephen C. Smith

Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, United Kingdom

Analogs of the novel herbicide, 5-*t*-butylcarbamoyloxy-3-(3-trifluoromethyl)phenyl-4-thiazolidinone **1**, were prepared and evaluated for herbicidal activity. A systematic structure-activity study around this novel toxophore revealed that a considerable degree of structural variation is tolerated without loss of biological activity. Optimum activity was observed when the central heterocyclic thiazolidinone ring was replaced by either by a pyrrolidinone or an oxazolidinone ring, and when the *t*-butylcarbamoyloxy substituent was replaced by a sterically hindered *N*-linked amide unit.

Recently, we reported that 5-*t*-butylcarbamoyloxy-3-(3-trifluoromethyl)-phenyl-4-thiazolidinone **1** is a representative member of a new class of *N*-aryl lactam herbicides which act by inhibiting incorporation of cellulose into cell wall material (*1,2*). Compound **1** is an experimental herbicide which shows potential for pre-emergence control of a wide range of grass and broad-leaved weeds, and which shows excellent selectivity to soybeans (*1*).

This paper reports the results of a study to elucidate the structure-activity relationships for this novel class of herbicides. Results are presented in three parts: variation of the aromatic and carbamate substituents; replacement of the thiazolidinone ring with alternative heterocycles; and replacement of the carbamate unit with isosteric groups. All compounds are racemic.

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

Synthesis and Herbicidal Activity of Thiazolidinone Analogs

The synthesis of compound **1** is illustrated in Figure 1. The starting thiazolidinone **2** was constructed by the cyclocondensation of 3-trifluoromethylaniline with thioglycolic acid and aqueous formaldehyde. Compound **2** was then hydroxylated by a two-stage procedure comprising an initial chlorination with sulfuryl chloride followed by hydrolysis to the 5-hydroxythiazolidinone **3**. Carbamoylation of **3** using *t*-butyl isocyanate then afforded the thiazolidinone carbamate **1**. Analogs of **1** bearing different substituents on the aromatic ring were prepared from the appropriate aniline by the same method. Similarly, analogs of **1** bearing different carbamate *N*-substituents were prepared by reaction of the hydroxythiazolidinone **3** with the appropriate isocyanate; alternatively *N,N*-dialkyl carbamates were prepared by carbamoylation of **3** with carbamoyl chlorides (*2*).

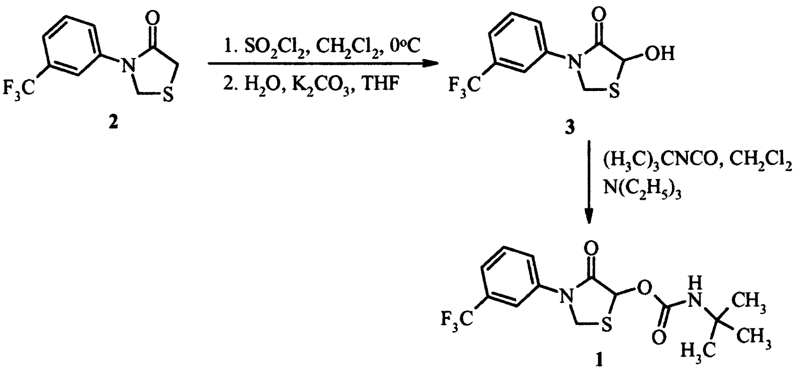


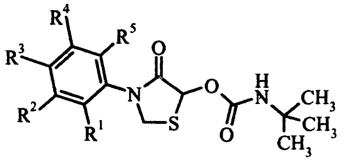
Figure 1. Preparation of thiazolidinone carbamate 1

The pre-emergence herbicidal activity of each of the new compounds was determined in the glasshouse. Seeds of *Setaria viridis* (green foxtail), *Panicum dichotomiflorum* (Fall panicum), *Echinochloa crus-galli* (barnyardgrass), *Chenopodium album* (fat hen) and *Amaranthus retroflexus* (redroot pigweed) were sown in a loamy sand at a depth of 1 cm. The formulated compounds were sprayed at a range of application rates, and treated plants were assessed 20 days after application by comparison with untreated plants.

In order to readily compare compounds, an overall assignment of herbicidal activity was made based on the application rate required to provide >90% control of all of the weed species. The scoring system used is as follows:

* * * * * *	weed control at 32-63 g ha^{-1}
* * * * *	weed control at 64-125 g ha^{-1}
* * * *	weed control at 126-250 g ha^{-1}
* * *	weed control at 251-500 g ha^{-1}
* *	weed control at 501-1000 g ha^{-1}
*	weed control at > 1000 g ha^{-1}
(*)	suppression of some weed species at >1000 g ha^{-1}

Table 1. Effects of aromatic substitution pattern on herbicidal activity for analogs of 1



Compound	*R^1*	*R^2*	*R^3*	*R^4*	*R^5*	*Herbicidal activity^1*
1	H	CF_3	H	H	H	* * * *
2	H	H	H	H	H	(*)
3	H	F	H	H	H	*
4	H	Cl	H	H	H	* * *
5	H	Br	H	H	H	* *
6	H	CH_3	H	H	H	* *
7	H	CN	H	H	H	*
8	H	NO_2	H	H	H	*
9	H	OCF_3	H	H	H	* * * *
10	Cl	H	H	H	H	(*)
11	H	H	Cl	H	H	*
12	H	CF_3	F	H	H	* * *
13	H	CF_3	Cl	H	H	* *

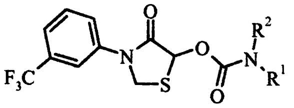
---

[1] see text for explanation of scoring system

The herbicidal activities of compounds in which the aromatic substitution pattern has been varied are summarized in Table 1. The very weak activity of compound **2**, which lacks the 3-trifluoromethyl substituent, indicates that a 3-substituent is crucial for activity. The activities of compounds **3** – **9**, which bear alternative 3-substituents, show that lipophilic, electron-withdrawing groups provide optimum activity, with the trifluoromethoxy-derivative **9** matching the activity of compound **1**. The fact that compound **6** is more active than **7** and **8** perhaps suggests that a 3-substituent with a lipophilic nature is preferable to an electron-withdrawing group with polar characteristics.

The results for compounds **10** and **11** clearly show that placing a chloro-substituent at the 2- or 4-position, respectively, leads to reduced activity compared to the 3-chloro analog **3**. The activity of compound **12** indicates that an additional fluoro-substituent can be tolerated at the 4-position, though activity is reduced for the corresponding 4-chloro analog **13**. Moderate activity was also seen for some 3,5-disubstituted analogs (*2*).

Table 2. Effects of carbamate *N*-substituents on herbicidal activity for analogs of 1



Compound	*R^1*	*R^2*	*Herbicidal Activity*[1]
14	$C(CH_3)_3$	CH_3	*
15	$CH(CH_3)_2$	H	*
16	CH_2CH_3	H	(*)
17	$C(CH_3)_2CH_2CH_3$	H	* * *
18	$C(CH_3)_2CH{=}CH_2$	H	* * * *
19	$C(CH_3)_2C{\equiv}CH$	H	* * * *
20	$C(CH_3)_2C{\equiv}CCH_3$	H	* * *
21	$C(CH_3)_2C_6H_5$	H	*
22	$C(CH_3)_2CN$	H	*

[1] see text for explanation of scoring system

The herbicidal activities of compounds in which the carbamate *N*-substituents have been varied are shown in Table 2. The result for compound **14** shows that the effect of *N*-methylation of **1** is to significantly reduce herbicidal activity; this was also seen for other *N,N*-dialkylated analogs (*2*). Intriguingly, replacing the *t*-butyl group of **1** with *i*-propyl (**15**) or ethyl (**16**) also dramatically reduces activity, demonstrating a preference for a tertiary alkyl group at this position. Looking at higher homlogs, the *t*-pentyl analog **17** is somewhat less active than **1**, though activity is partially restored for the corresponding olefin **18** and acetylene **19**. However, further homologation of **19** results in a lowering of activity (**20**). Both the dimethylbenzyl analog **21** and the dimethylacetonitrile **22** showed very poor activity.

These initial SAR studies on analogs of **1** showed that optimum herbicidal activity is obtained when the aromatic ring bears a 3-substituent, with trifluoromethyl and trifluoromethoxy being preferred, and when the carbamate nitrogen is mono-substituted by a bulky substituent, preferably a *t*-butyl group.

Replacement of the Thiazolidinone Ring of Compound 1

The effect of replacing the thiazolidinone ring with other heterocyclic ring systems was investigated next. Compound **23** (Table 3), the pyrrolidinone analog of **1**, was prepared by the high temperature cyclocondensation of α-hydroxybutyrolactone with 3-trifluoromethylaniline to afford the corresponding α-hydroxypyrrolidinone **24** (Figure 2), which was then carbamoylated using *t*-butyl isocyanate to give **23** (*3*). Compound **25** (Table 3), the oxazolidinone analog of **1**, was prepared by the *t*-butyl isocyanate carbamoylation of the hydroxyoxazolidinone intermediate **26**, which was itself obtained in high yield from the hydroxythiazolidinone **3** by the novel one-step oxidative procedure outlined in Figure 2 (*4*). Further details of this interesting reaction will be reported elsewhere.

The imidazolidinone ring of compound **27** (Table 3) was constructed as shown in Figure 2. Reaction of 3-trifluoromethylphenyl isocyanate with *O*-benzylhydroxylamine afforded urea **28**, which underwent a double-alkylation with dibromoethane to give the imidazolidinone **29**. This then underwent hydrogenolytic deprotection to afford the *N*-hydroxy imidazolidinone **30**, which was carbamoylated using *t*-butyl isocyanate to give **27** (*2*). Compound **31** (Table 3), the 6-membered ring homolog of **1**, was prepared by a similar method to that used for the preparation of compound **1**, in that the ring was constructed first and subsequently hydroxylated. Thus, ethyl thioglycolate was alkylated with *N*-(2-bromoethyl)-3-trifluoromethylaniline, and the resultant aminoester was then cyclised to the 6-membered lactam by treatment with acid (*2*). This was then hydroxylated using the two-stage method illustrated in Figure 1 for the hydroxylation of **2**, and then carbamoylated using *t*-butyl isocyanate to give **31**.

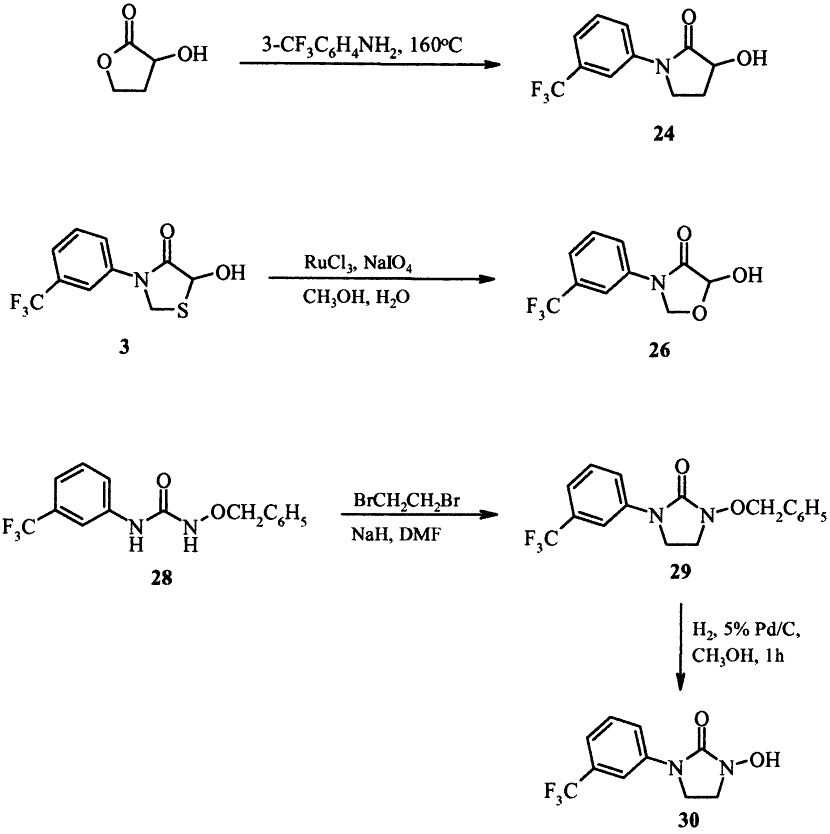
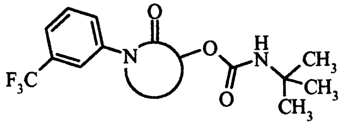
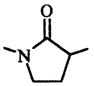
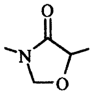
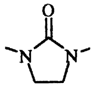
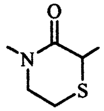


*Figure 2. Preparation of hydroxypyrrolidinone **24**, hydroxyoxazolidinone **26** and hydroxyimidazolidinone **30** intermediates*

The herbicidal activities of compounds **23**, **25**, **27** and **31** are shown in Table 3. As can be seen, the pyrrolidinone **23** and oxazolidinone **25** show similar levels of activity to the thiazolidinone **1**, controlling all the weeds in the test at between 125 and 250 g ha^{-1}. However, the imidazolidinone **27**, in which an sp^2 hybridised nitrogen atom has replaced the sp^3 carbon atom of pyrrolidinone **23**, shows much weaker activity; this suggests that the geometry at this position is important for effective binding to the receptor. Thiazinone **31**, the 6-membered homolog of **1**, shows only very weak herbicidal activity. The 6-membered homologs of **23**, **25**, and **27** also show very weak herbicidal activity (*2*).

Table 3. Effects of variation of the thiazolidinone ring on herbicidal activity



Compound	*Ring*	*Herbicidal Activity*[1]
23		* * * *
25		* * * *
27		* *
31		(*)

[1] see text for explanation of scoring system

Isosteric Replacement of the Carbamate Moiety

The effects of replacing the carbamate moiety were first investigated for a series of 3-trifluoromethoxypyrrolidinone derivatives, *i.e.* analogs of compound **9** (Table 1). The synthetic procedures used to prepare the compounds are illustrated in Figure 3. The pivotal bromopyrrolidinone intermediate **32** was prepared from 3-trifluoromethyoxyaniline and 2,4-dibromobutyryl chloride using a method analogous to that described by Okawara, Matsuda and Furukawa (*5*) for related *N*-substituted 3-bromopyrrolidinones. Reaction of **32** with methylamine afforded the methylaminopyrrolidinone **33**, which was then converted to the following compounds (Table 4) by treatment with the specified reagent (parentheses): carbamate **35** ((2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile); urea **37** (*t*-butyl isocyanate); urea **41** (*N*-*t*-butyl-*N*-methyl carbamoyl chloride); amide **43** (3,3-dimethylbutyryl chloride); amide **48** (3,3-dimethyl-2-oxobutyryl chloride); and amide **47** (2,2-dimethylpropionyl chloride). The *N*-ethyl derivatives, **38**, **44** and **48** (Table 4), and the *N*-*n*-propyl derivatives, **39** and **45** (Table 4), were prepared similarly by reaction of **32** with ethylamine and propylamine, respectively, and subsequent capping with the appropriate acylating or carbamoyating agent. The *NH*-derivatives, **34**, **36**, **40**, **42** and **46** (Table 4), were obtained from **32** by reaction with sodium azide, followed by 1,3-propanedithiol reduction of the resultant azido-pyrrolidinone to the amino-pyrrolidinone analogous to **33**, and subsequent acylation or carbamoylation, as described above for the *N*-methyl derivatives.

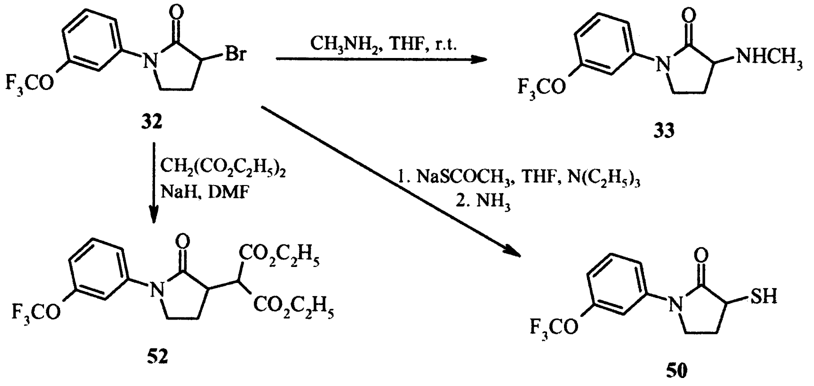
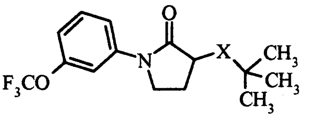


Figure 3. Methods used to prepare intermediates used in the syntheses of pyrrolidinone analogs in which the carbamate group has been varied

The thiolcarbamate **49** (Table 4) was prepared by the *t*-butyl isocyanate carbamoylation of the mercaptopyrrolidinone intermediate **50**, which was itself obtained from **32** by a two-step process involving reaction with mercaptoacetic acid followed by de-acetylation with ammonia (Figure 3). The carbon substituent of the *C*-linked amide **51** (Table 4) was inserted by reaction of the bromo-pyrrolidinone **32** with diethyl malonate to afford the diester intermediate **52** (Figure 3). This was hydrolysed to the diacid and then decarboxylated to give the corresponding mono-carboxylic acid. Conversion to the acid chloride with thionyl choride and reaction with *t*-butylamine then afforded the amide **51**.

Table 4. Effects of variation of the carbamate unit on herbicidal activity for a series of pyrrolidinones



Compound	*X*	*Activity*[1]	*Compound*	*X*	*Activity*[1]
9	O-CO-NH	* * * *	**42**	NH-CO-CH_2	* * *
34	NH-CO-O	* *	**43**	NCH_3-CO-CH_2	* * * * *
35	NCH_3-CO-O	* * *	**44**	NC_2H_5-CO-CH_2	* * * * *
36	NH-CO-NH	* *	**45**	NC_3H_7-CO-CH_2	* * *
37	NCH_3-CO-NH	* * * * *	**46**	NH-CO	*
38	NC_2H_5-CO-NH	* * * *	**47**	NCH_3-CO	* * * * *
39	NC_3H_7-CO-NH	* * *	**48**	NC_2H_5-CO	(*)
40	NH-CO-NCH_3	*	**49**	S-CO-NH	* *
41	NCH_3-CO-NCH_3	* *	**51**	CH_2-CO-NH	* * *

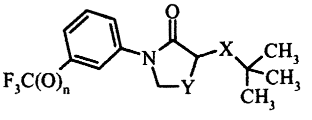
[1] see text for explanation of scoring system

Compound **34**, in which the carbamate linking group has been reversed, shows reduced herbicidal activity relative to **9**. Activity is restored somewhat for the *N*-methylated carbamate **35**, though the overall activity is still less than for **9**. A similar trend is also seen for the series of ureas **36** – **39**, in that the *N*-alkylated derivatives show stronger herbicidal activity than the *NH* analog; optimum activity is observed for the *N*-methyl analog **37**, which shows higher activity than the carbamate **9**, and activity falls off gradually on moving to the *N*-ethyl (**38**) and *N*-propyl (**39**) substitutents, indicating a size constraint at this position. Compound **40**, the isomer of **37** shows poor activity, which is improved slightly on moving to the *N,N'*-dimethyl substituted compound **41**.

A smooth gradation of herbicidal activity is observed for the series of *N*-linked amides **42** – **45**, with optimum activity being seen with the *N*-methyl and *N*-ethyl analogs **43** and **44**; as for the urea **37**, these compounds show more potent herbicidal activity than the corresponding carbamate **9**. In contrast, activity in the series of 'shortened' *N*-linked amides **46** – **48** is much tighter, with excellent herbicidal activity being observed for the *N*-methyl analog **47**, but only very poor activity for the *NH* and *N*-ethyl analogs **46** and **48**, respectively; presumably this is due to steric crowding restricting the conformations that these compounds may adopt. The thiolcarbamate **49** and *C*-linked amide **51** both show reduced activity relative to the carbamate **9**.

The excellent herbicidal activities of the pyrrolidinone amides **44, 45** and **47**, and the urea **37**, prompted us to prepare their thiazolidinone and oxazolidinone counterparts. Thiazolidinones **53** – **56** (Table 5) were prepared from the 5-chlorothiazolidinone by reaction with methylamine or ethylamine, followed by reaction with the appropriate acid chloride or isocyanate. Similarly, oxazolidinones **57** – **60** (Table 5) were prepared by converting the 5-hydroxyoxazolidinone to the corresponding 5-chloro-oxazolidinone, which then gave the target compounds on aminolysis and acylation or carbamoylation (*3*).

Table 5. Herbicidal activities of thiazolidinone and oxazolidinone amide and urea derivatives



Compound	*n*	*Y*	*X*	*Herbicidal activity*[1]
53	1	S	NCH_3-CO-CH_2	* * * * *
54	1	S	NC_2H_5-CO-CH_2	* * *
55	1	S	NCH_3-CO	* * * * *
56	0	S	NCH_3-CO-NH	* * *
57	1	O	NCH_3-CO-CH_2	* * * * * *
58	1	O	NC_2H_5-CO-CH_2	* * * * * *
59	1	O	NCH_3-CO	* * * * * *
60	0	O	NCH_3-CO-NH	* * * *

---

[1] see text for explanation of scoring system

The herbicidal activities of compounds **53** – **60** are shown in Table 5. For the series of thiazolidinones **53** – **56**, the herbicidal activities shown by the *N*-methylamides **53** and **55** match those of the corresponding pyrrolidinones **43** and

47, although reduced activity, relative to the analogous pyrrolidinones, is seen for both the *N*-ethylamide **54** and the *N*-methyl urea **56**. However, for the oxazolidinones, excellent herbicidal activity is seen for the amides **57** – **59**, each of which are more potent herbicides than the corresponding pyrrolidinones, controlling all of the weed species at 32 – 63 g ha^{-1}; these are the most potent herbicides reported in this paper. In contrast, the oxazolidinone urea **60** is less active than its pyrrolidinone counterpart **37**.

Conclusions

A detailed structure-activity study around the novel herbicide, 5-*t*-butylcarbamoyloxy-3-(3-trifluoromethyl)phenyl-4-thiazolidinone revealed that a considerable degree of structural variation is tolerated without total loss of herbicidal activity. A lipophilic, electron-withdrawing substituent at the 3-position of the aromatic ring is essential for good herbicidal activity, with trifluoromethyl and trifluoromethoxy being the preferred groups. A tertiary alkyl *N*-substituent on the carbamate moiety is also required for good activity, with *t*-butyl being a preferred substituent; additional substitution on the carbamate nitrogen results in reduced activity. Replacement of the thiazolidinone ring system with either a pyrrolidinone or oxazolidinone ring system resulted in enhanced herbicidal activity, though replacement with either a 6-membered thiazolidinone analog or a 5-membered imidazolidinone ring resulted in a significant loss in activity. Herbicidal activity is maintained when the carbamate function is replaced by a wide range of alternative groups, with *N*-linked amides and ureas providing the most potent activity. Oxazolidinone *N*-linked amides were found to be the most potent herbicides.

Acknowledgments

The authors are indebted to Sarah Murfitt, Sue Janeway, Jane Townson and Stott Howard for the detailed herbicidal activity determinations.

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Chapter 4

3-(Heterocyclyl)phenyl Cyanurates: Synthesis and Herbicidal Activity

Gary M. Karp, A. Don Crews, Mark C. Manfredi, Axel Kleemann, Robert L. Arotin, Matthew L. Crawley, Brian Dahlke, and Roger Baerg

BASF Agro Research, P.O. Box 400, Princeton, NJ 08543–0400

3-(Heterocyclyl)phenyl cyanurates **1**, a novel class of protoporphyrinogen oxidase (protox) inhibitors were prepared and evaluated for their herbicidal activity. The compounds were primarily postemergence broadleaf compounds. The structure-activity relationships for herbicidal activity derived from modification of the substituents on the cyanurate ring and phenyl ring and as well as the heterocycle portion of the molecule is the current focus of this chapter.

Compounds that inhibit protoporphyrinogen oxidase (protox) (*1*, *2*), a key enzyme in the tetrapyrrole biosynthetic pathway, comprise perhaps the largest class of new chemical entities as well as accounting for a large portion of patent filings among the known herbicide modes of action disclosed in recent years (*3*). A number of factors would seem to account for this: the relatively low reported use rates, the absence of any significant development of weed resistance and the fact that a large number of structural types inhibit protox. The two major chemical classes that account for the bulk of protox inhibitors reported to date include the diphenyl ethers and the cyclic imides (which include the related aryl

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
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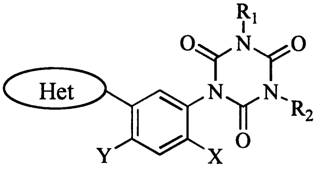
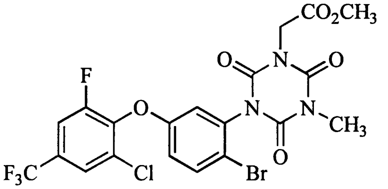
heterocycles) (*4-6*). The accepted wisdom is that these structural classes mimic two or three rings of the tetrapyrrole molecule although the different classes likely bind with different orientations at the receptor site (*6*, *7*).

With the discovery of the potent herbicidal activity of the aryloxy phenyl cyanurates **2** (*8*) we immediately recognized that replacing the aryloxy portion in **2** with a tetrahydrophthalimide (THP) or other related heterocyclic moiety should result in compounds that also inhibit protox. A full exploratory synthesis program was then undertaken to determine the scope of the activity of these compounds.

A systematic SAR study was conducted by examining three major structural modifications: substitution in the phenyl ring, substitution in the cyanurate ring and variation of the heterocycle.



1



2

Synthesis

Optimization of central ring substituents.

Entry to the various halogenated phenyl substituents was carried out in one of two manners. Halogenated anilines **3** were converted to the ureas **5** upon treatment with methyl isocyanate. Alternatively, halogenated benzamides **4** were converted to **5** via Hoffmann degradation followed by treatment with methylamine (Figure 1). Cyclization of the ureas with N-(chlorocarbonyl)-isocyanate afforded the cyanurates **6**. Nitration followed by reduction gave the anilines **8**. Heating the anilines with tetrahydrophthalic anhydride afforded the THP analogs **9**. Finally, alkylation with methyl bromoacetate gave the initial series of target compounds **10**. Upon greenhouse evaluation, it was shown that the most active analogs both post- and preemergence comprised substitution in which X is F and Y is Cl or Br. Since the less expensive chloro analog was more readily obtained, all further synthetic work was carried out with the chloro analog.

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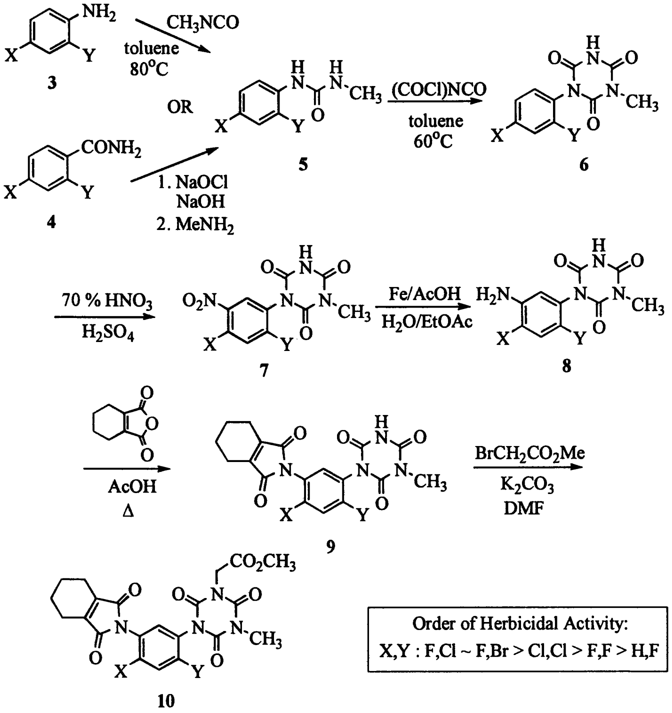
3
4
5
6
7
8
9
10
CH3NCO
toluene
80°C
OR
1. NaOCl
NaOH
2. MeNH2
(COCl)NCO
toluene
60°C
70 % HNO3
H2SO4
Fe/AcOH
H2O/EtOAc
AcOH
Δ
BrCH2CO2Me
K2CO3
DMF
Order of Herbicidal Activity:
X,Y : F,Cl ~ F,Br > Cl,Cl > F,F > H,F

Figure 1. Preparation of halogenated tetrahydrophthalimide phenyl cyanurates.

Optimization of the ester group was then carried out. The homologous series of alkyl bromoacetates (methyl to *tert*-butyl) was prepared. The isopropyl and *tert*-butyl esters conferred the most activity. For convenience, subsequent structural modification utilized the isopropyl ester.

Optimization of the cyclic imide moiety

Preparation of the key intermediates for the various heterocyclyl phenyl cyanurates is shown in Figure 2. Benzamide **11** was converted to the urea **12** via a Hoffmann rearrangement. Cyclization with N-(chlorocarbonyl)isocyanate gave **13**. Initially, the N-alkylation step was carried out to give **14** followed by nitration. The strongly acidic media used in the nitration led to ester hydrolysis (**15**). Fischer esterification then gave **16**. By reversing the nitration and N-alkylation steps, **16** was obtained in two steps (via **17**) without the need for reesterification. Nitro reduction gave the key aniline intermediate **18**. Two other important heterocyclic building blocks prepared were the isocyanate **19** and isothiocyanate **20**, prepared from the treatment of **18** with phosgene and thiophosgene, respectively. From these building blocks, a select number of imide and isoimide-type heterocycles that have been reported in the protox literature were prepared to evaluate the structure-activity profile for this class.

Imidazo[1,5,a]pyridine-1,3-diones, Imidazo[5,1-c][1,4]oxazine-1,3-diones and Imidazo[5,1-c][1,4]thiazine-1,3-diones.

A series of imide-type heterocycles containing one bridgehead nitrogen atom were prepared as shown in Figure 3. Treatment of commercially available ethyl pipecolinate with isocyanate **19** in toluene at reflux gave the imidazo[1,5,a]pyridine-1,3-dione analog **21**. In similar fashion, treatment of **19** with ethyl morpholinecarboxylate (*9*) gave the imidazo[5,1-c][1,4]oxazine-1,3-dione **22** analog. Likewise, reaction with ethyl thiomorpholinecarboxylate (*10*) gave the imidazo[5,1-c][1,4]thiazine-1,3-dione **23**. Oxidation of the sulfur atom afforded the sulfoxide **24**.

[1,3,4]Thiadiazolo[3,4-a]pyridazines, [1,3,4]thiadiazolo[3,4-a]1,2-diazepines, [1,3,4]oxadiazolo[3,4-a]pyridazines and [1,2,4]triazolo[1,2-a]pyridazines.

Imide and isoimide type heterocycles containing two bridgehead nitrogen atoms were also prepared (Figure 4). Reaction of isothiocyanate **20** with the pyridazine **25a** or diazepine **25b** in methanol gave the six- and seven-membered thiosemicarbazide analogs **26** and **27**, respectively. Cyclization of the semicarbazides with phosgene or thiophosgene gave the target thiadiazolopyridazines and thiadiazolodiazepines **28-31** (*10*) with an exocyclic carbonyl or thiocarbonyl group.

Treatment of the isocyanate **19** with the pyridazine **25a** in methanol gave not the semicarbazide **32** but the carbamate **33** exclusively (Figure 5). Apparently, the greater reactivity of the isocyanate vs. the isothiocyanate caused competitive reaction with the solvent methanol. This was overcome by switching to the non-nucleophilic solvent dichloroethane, affording the semicarbazide **32**. Cyclization of **32** with thiophosgene gave the triazolopyridazine analog **34**. In contrast, cyclization with diphosgene gave not the triazolopyridazine **35** but the oxadiazolopyridazine **36** as the sole isolable product.

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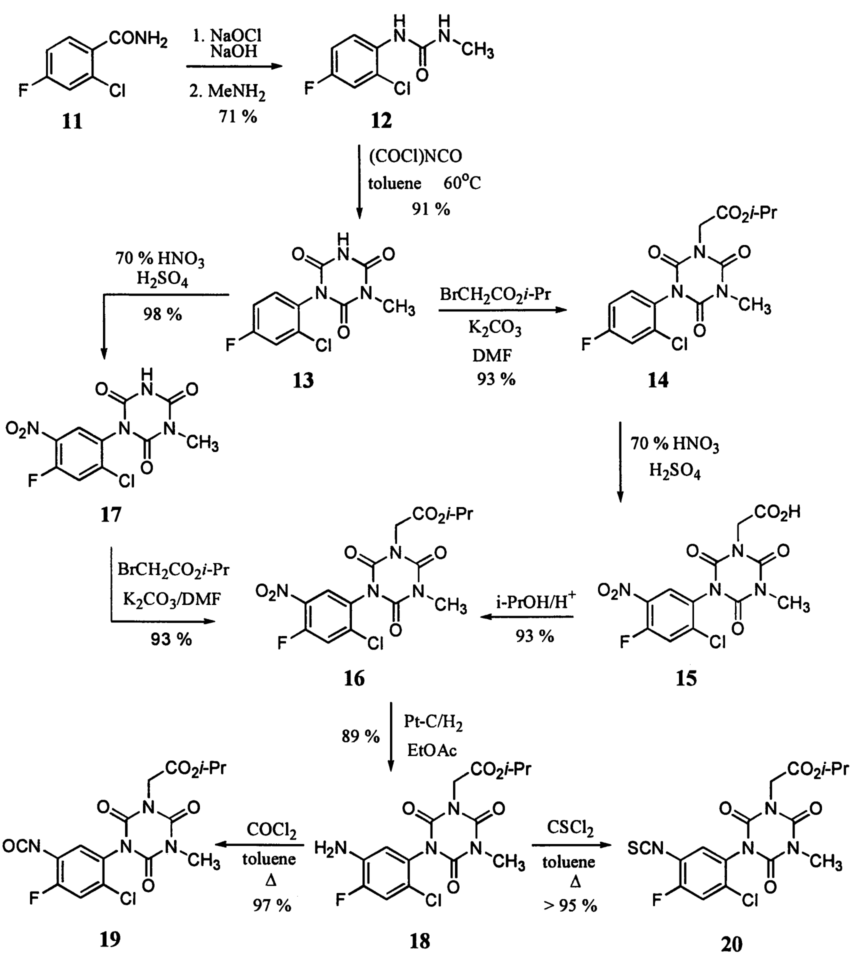
11
1. NaOCl NaOH
2. MeNH2
71 %
12
(COCl)NCO
toluene 60°C
91 %
70 % HNO3
H2SO4
98 %
13
BrCH2CO2i-Pr
K2CO3
DMF
93 %
14
17
70 % HNO3
H2SO4
BrCH2CO2i-Pr
K2CO3/DMF
93 %
16
i-PrOH/H+
93 %
15
Pt-C/H2
EtOAc
89 %
COCl2
toluene
Δ
97 %
CSCl2
toluene
Δ
> 95 %
19
18
20

Figure 2. Preparation of phenyl cyanurate intermediates.

Dihydro[1,3,4]thiadiazolo[3,4-a]pyridazines

Satow *et. al.* (*11*) have disclosed a series of unsaturated [1,3,4]thiadiazolo[3,4-a]pyridazines as potent protox inhibitors. To further elucidate the structure-activity profile of the heterocycles attached to the phenyl ring we targeted the preparation of dihydro[1,3,4]thiadiazolo[3,4-a]pyridazines for comparison with the other heterocycles (Figure 6). Treatment of isothiocyanate **20** with tetrahydropyridazine (*11*) gave the thiosemicarbazide **37**.

Cyclization with phosgene or thiophosgene gave the dihydro[1,3,4]thiadiazolo-[3,4-a]pyridazines **38** and **39**, respectively.

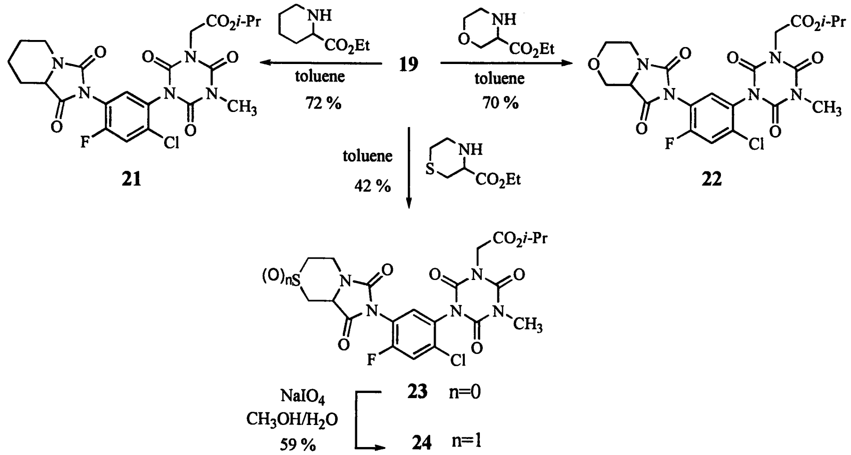
21
toluene
72 %
19
toluene
70 %
22
toluene
42 %
NaIO4
CH3OH/H2O
59 %
23 n=0
24 n=1

Figure 3. Preparation of Imidazo[1,5,a]pyridine-1,3-diones, imidazo[5,1-c][1,4]oxazine-1,3-diones, and imidazo[5,1-c][1,4]thiazine-1,3-diones.

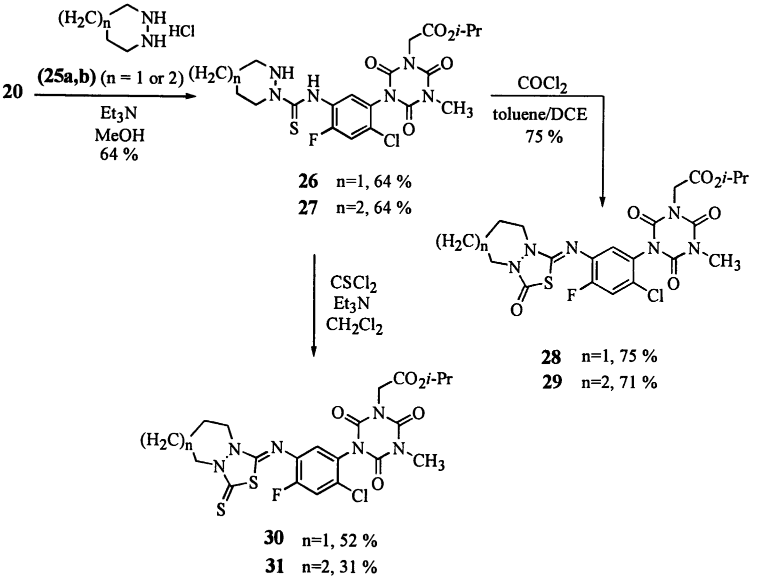
20
(25a,b) (n = 1 or 2)
Et3N
MeOH
64 %
26 n=1, 64 %
27 n=2, 64 %
COCl2
toluene/DCE
75 %
28 n=1, 75 %
29 n=2, 71 %
CSCl2
Et3N
CH2Cl2
30 n=1, 52 %
31 n=2, 31 %

Figure 4. Preparation of [1,3,4]Thiadiazolo[3,4-a]pyridazines and [1,3,4]thiadiazolo[3,4-a]1,2-diazepines.

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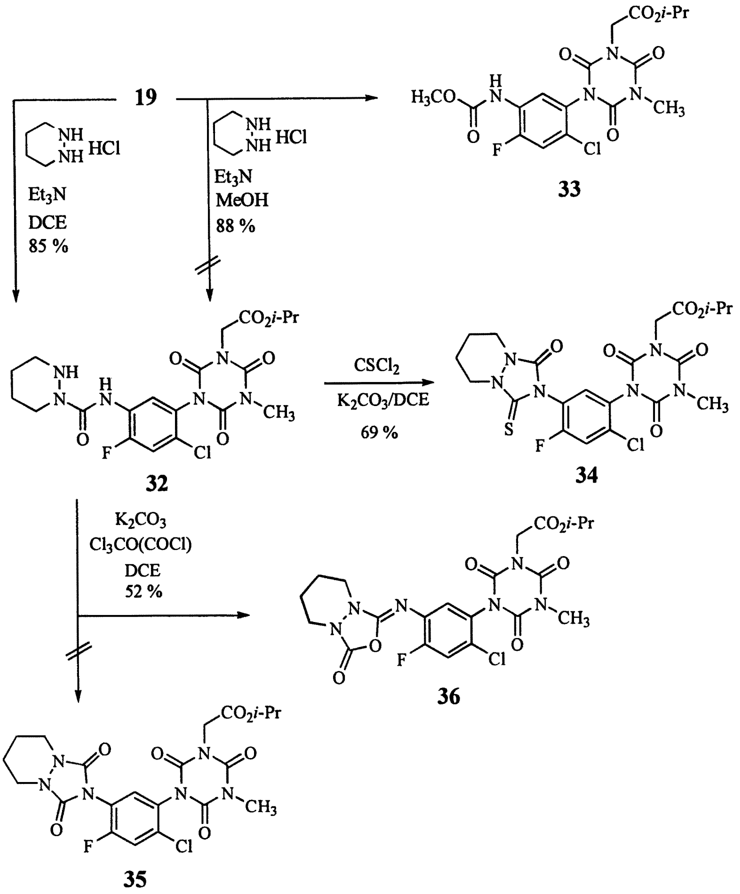
19
NH
NH
HCl
Et3N
DCE
85 %
NH
NH
HCl
Et3N
MeOH
88 %
33
32
CSCl2
K2CO3/DCE
69 %
34
K2CO3
Cl3CO(COCl)
DCE
52 %
36
35

Figure 5. Preparation of [1,3,4]oxadiazolo[3,4-a]pyridazines and [1,2,4]triazolo[1,2-a]pyridazines.

Uracil ring

Literature reports indicate that incorporation of a 4-trifluoromethyl-substituted uracil ring often leads to increased preemergence activity (*12*, *13*). To determine whether we could increase the preemergence activity of the phenyl cyanurates, the requisite N-methyl uracil analog **41** was prepared in two steps (Figure 7). The isocyanate **19** was reacted with ethyl 3-amino-4,4,4-trifluorocrotonate to give **40** which was alkylated to afford the desired target **41**.

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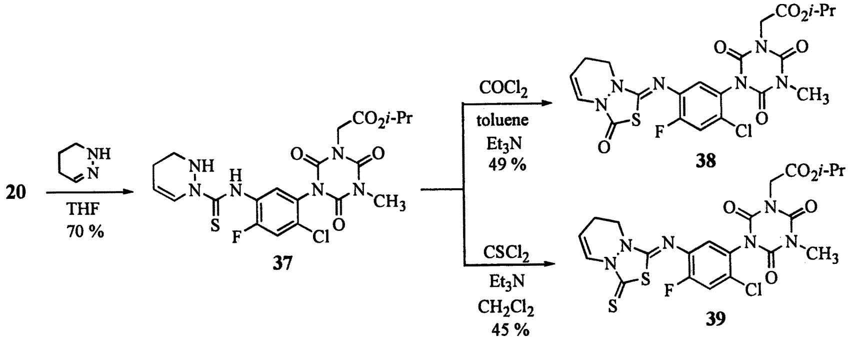
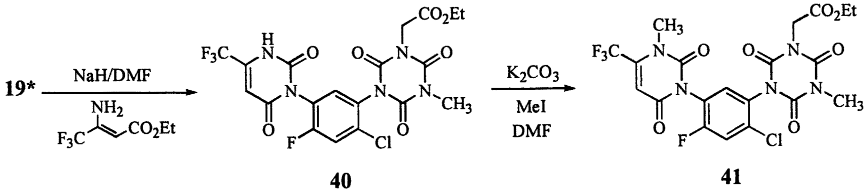


Figure 6. Dihydro[1,3,4]thiadiazolo[3,4-a]pyridazines.



*Ethyl ester of compound **19**

Figure 7. Preparation of uracil phenyl cyanurate.

Herbicidal Activity

Each of the compounds prepared were evaluated in a greenhouse assay both post- and preemergence at rates between 32 g/ha and 1000 g/ha. All of the compounds tested exhibited greater activity towards broadleaf weeds than grass weeds. In addition most of the compounds were more active on postemergence application. In the comparisons below, the herbicidal activity is reported as the average rate (g/ha) necessary to control the six broadleaf weeds tested. These include velvetleaf (*Abutilon theophrasti*), ragweed (*Ambrosia artemisiifolia*), sicklepod (*Cassia obtusifolia*), lambsquarters *(Chenopodium album*), galium (*Galium aparine*) and morningglory spp. *(Ipomea spp.*).

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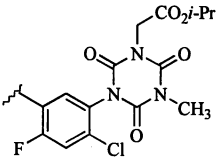
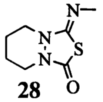
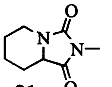
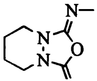
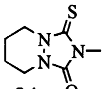
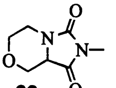
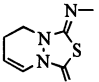
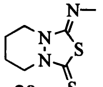
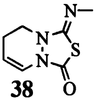
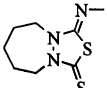
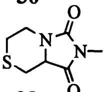
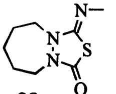
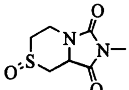
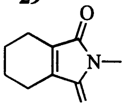
Optimization of the heterocycle portion.

The most potent heterocycles examined were the thiadiazolopyridazine **28** and the triazolopyridazine **34** controlling the broadleaf weeds at an average rate of 32 g/ha (Table 1). The interconversion of compounds such as **28** to **34** is known (*11*) (Dimroth rearrangement) and it can not be ruled out that the comparable level of activity is indeed due to such an interconversion *in vivo*. Replacing the thiadiazolopyridazine exo carbonyl by a thiocarbonyl (**28** vs. **30**) decreases activity by about half while replacing the ring sulfur by an oxygen (**28** vs. **35**) decreases activity nearly sixteen-fold. Unsaturation of the thiadiazolopyridazines decreases activity nearly eight-fold (**28** and **30** vs. **38** and **39**) while ring expansion of the thiadiazolopyridazines to thiadiazolodiazepines likewise results in an eight-fold decrease in activity (**28** and **30** vs. **29** and **31**).

Table 1. Average Broadleaf Postemergence Control Rates (g/ha).

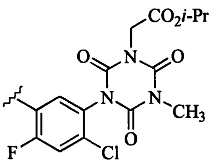


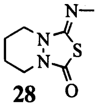
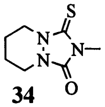
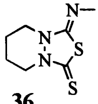
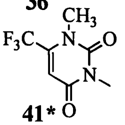
	POST (g/ha)		*POST (g/ha)*		*POST (g/ha)*
 **28**	32	 **21**	250	 **36**	500
 **34**	32	 **22**	250	 **39**	500
 **30**	63	 **38**	250	 **31**	500
 **23**	125	 **29**	250	 **24**	>500
		 **10**	250		

Among the fused imidazole systems, imidazothiazine **23** was the most potent, controlling the broadleaf weeds at 125 g/ha. The oxygen (**22**) and carbon analogs (**21**) were only half as active. Oxidation of the ring sulfur (**24**) reduced activity greatly.

The uracil analog **41** is compared to the most active postemergence analogs in Table 2. While not the most active postemergence, **41** was the most active preemergence compound prepared in this series. Among the other heterocyclic analogs evaluated, only the thiadiazolopyridazine **28** exhibited any reasonable level of preemergence activity.

Table 2. Comparison of Average Broadleaf Control Rates (g/ha).



	POST (g/ha)	*PRE (g/ha)*
 **28**	32	250
 **34**	32	>1000
 **36**	63	>1000
 **41***	125	125

*Ethyl ester

Optimization of the Cyanurate Substituents

In the preceeding examples, the heterocyclic replacements were carried out by keeping the cyanurate N-substituents constant (based on the earlier THP

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In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

analog). The thiadiazolopyridazine **28**, one of the most active analogs, was then subjected to further structural modification to ascertain whether activity could be further improved. Replacement of the N-methyl by other substituents (*e.g.*, methoxymethyl, allyl, cyanomethyl, benzyl or a second ester moiety) resulted in a uniform decrease in activity. Likewise, replacing the isopropyl acetic ester group with other substituents (*e.g.*, allyl, propargyl) also resulted in a decrease in activity.

Conclusion

The 3-(heterocyclyl)phenyl cyanurates described in this paper are primarily postemergence broadleaf compounds. Due to the limitations of weed spectrum and insufficient crop tolerance these compounds were not developed further.

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Chapter 5

Synthesis of Heterocyclic Analogs of Herbicidal Aryl Triazolinones

Colin M. Tice and Adam C-T. Hsu

Rohm and Haas Company, 727 Norristown Road, Spring House, PA 19477–0904

1-*t*-Butyl-3-phenyl-4-propargyl-1,2,4-triazolin-5-one **1** possesses lead level herbicidal activity. In an effort to improve the activity of the lead compound, a series of analogs varying in the heterocylic portion of the molecule was synthesized. Three bioisosteric heterocycles, 5-phenyl-4-propargyl-2-propylisoxazolidin-3-one **16**, 2,3-dimethyl-6-phenyl-5-propargyl-4(3H)-pyrimidinone **25** and 5,6-dimethyl-2-phenyl-3-propargyl-4(3H)-pyrimidinone **27**, were discovered. The last of these offered a superior starting point for further analog synthesis.

Phenyl triazolinone RH 88488 (1, Figure 1) was synthesized as part of a program to explore the utility of t-butylhydrazine as a building block for agrochemical synthesis (1). Upon greenhouse screening, the compound's broad spectrum preemergence herbicidal activity immediately attracted attention. New leaf tissue in treated plants was white, a symptom commonly observed with herbicides that interfere with carotenoid biosynthesis. Indeed analysis of affected leaf tissue showed an increase in the carotenoid precursors phytoene, phytofluene and zeta carotene (2). A literature search revealed that workers at Nihon Nohyaku had previously investigated some similar

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
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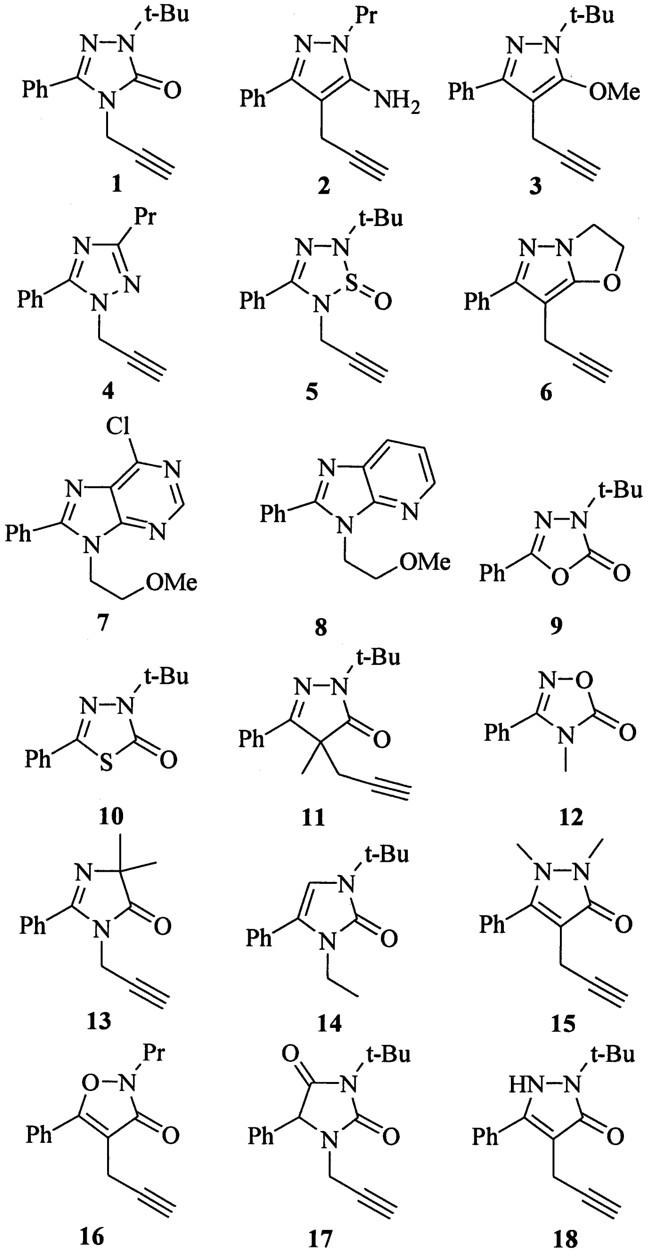

Figure 1. Heterocyclic Analogs of Phenyl Triazolinone Herbicide 1

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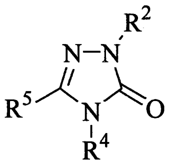
compounds (*3*). The level of activity of **1** was such that it advanced through the greenhouse screening cascade and was submitted for field testing in several key agronomic crops where it showed good activity preemergence against a number of weeds at 4800 g ha^{-1}. Cotton and sunflower were tolerant of the compound. In our experience, it is rather unusual that the initial lead in a new series is sufficiently active to warrant field testing.

The SAR of the substituents around the triazolinone ring of **1** was investigated. The conclusions of this study are summarized in Figure 2. None of the analogs synthesized was superior to **1**, although several were comparable. The greatest flexibility was found at R^2, the *t*-butyl position in **1**, where other similarly sized, hydrophobic substituents retained activity. There was a stringent requirement for a propargyl group at R^4 for good activity. Fluorine substitution was tolerated at the 2- and 3-positions of the phenyl ring but larger substituents at these positions and any substitution at the 4-position, including fluorine, diminished activity.



R^2 t-Bu, $CH_2C{\equiv}CH$, n-Pr, CH_2CF_3 > n-Bu, i-Bu > Et > Me

R^4 $CH_2C{\equiv}CH$ > CH_2CH_2OMe > Et > CH_2OMe > Me
$CH_2C{\equiv}CH$ >> $CH_2CH{=}CH_2$ > n-Pr

R^5 = Ph, 2-F-Ph, 3-F-Ph > 2-thienyl > 3-thienyl
>> naphthyl, pyridyl, 2-furyl

Figure 2. Summary of Triazolinone Substituent SAR

Five Membered Heterocycle SAR and Model Development

In parallel with the effort to optimize the substituents, compounds in which the core triazolinone ring was replaced with other 5-membered heterocycles were targeted for synthesis. Wherever possible the optimal substituents (R^2 = t-Bu, R^4 = $CH_2C{\equiv}CH$, R^5 = Ph) were maintained around the new 5-membered ring; however, in the interests of synthetic expediency suboptimal substituents (R^4 = methyl, ethyl, methoxymethyl or 2-methoxyethyl in place of propargyl; R^2 = n-propyl or methyl in place of *t*-butyl) were used in some cases. Of course, in these cases the activity of the resulting heterocyclic analog was compared to that of the identically substituted triazolinone. The structures of heterocyclic analogs made are shown in Figure 1. In general literature procedures were adapted to the synthesis of these compounds (*4*) and they were tested in the greenhouse at 4800 g ha^{-1}. When the carbonyl group of **1** was replaced with

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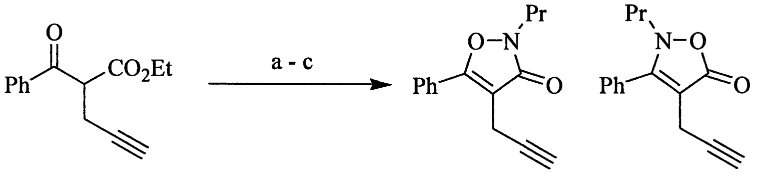
other functional groups capable of forming a hydrogen bond, amino in **2**, methoxy in **3**, sp^{2}N in **4** and sulfoxide in **5** (*5*), only the last compound retained any herbicidal activity and it was much less active than **1**. Tying the carbonyl group back into a ring as an ether in **6** or an imino group in **7** and **8** abolished activity. Compounds **9** and **10** in which the N^4-propargyl unit was deleted and replaced with an oxygen or sulfur atom were inactive. Pyrazolinone **11** in which the propargyl group was retained but N^4 was replaced with a CMe unit was inactive. Replacement of the N^2-t-Bu moiety with an oxygen atom in **12** or CMe$_2$ in **13** abolished activity. The inactivity of **11** and **13** suggested that the heterocyclic the substituents. N^1 of the triazolinone was replaced with CH in **14**, NMe in **15**, O in **16**, C=O in **17** and NH in **18**; the ether oxygen replacement in isoxazolidinone **16** successfully retained a substantial level of activity. The regioselective synthesis of **16** from β-ketoester **19** and N-propylhydroxylamine, following the method of Sato *et al* (*6*), is depicted in Figure 3.



19 **16** **20**

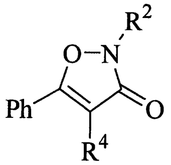
a) NaOH, aq MeOH, -20°C. b) PrHNOH, -20°C. c) conc HCl, reflux.

Figure 3. Isoxazolidinone Synthesis

A small group of analogs of **16** was prepared to investigate the SAR of this series (*7*). Structures and greenhouse data for these compounds are shown in Table I. Compound **21**, in which the Pr group was replaced with Me, retained activity while replacement of the propargyl group with hydrogen in **22** or ethoxycarbonyl in **23** abolished activity. This results of this limited SAR study paralleled those observed in triazolinone series.

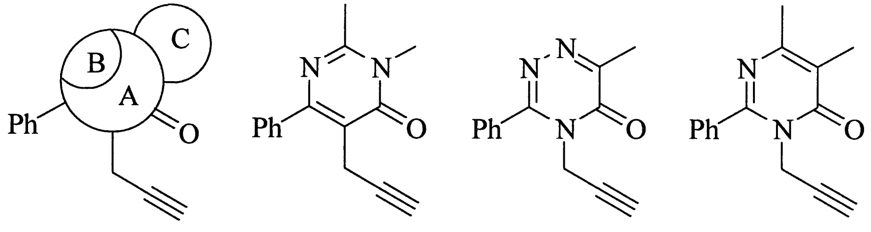
Consideration of the activity of the compounds in Figure 2 allowed us to propose the model for herbicidal activity shown as **24** in Figure 4. Key features of the model are the requirements for a planar heterocycle (A) incorporating a carbonyl group, a hydrogen bond acceptor distal from the carbonyl group (B) and open valencies in the appropriate positions to accommodate the phenyl, propargyl and hydrophobic (C) moieties. To test the predictive power of the model the three 6-membered ring heterocycles **25** - **27** (Figure 4) were synthesized and tested.

Table I. Preemergence Herbicidal Activity of Isoxazolidinone Analogs



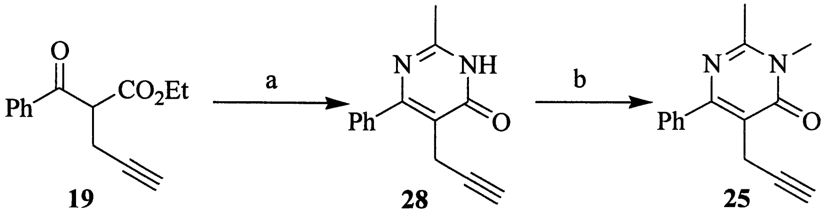
Compd	*R^2*	*R^4*	*AM*[a]	*AD*[b]
16	*n*-Pr	CH$_2$C≡CH	62	70
21	Me	CH$_2$C≡CH	61	50
22	Me	H	0	0
23	*t*-Bu	CO$_2$Et	0	0

[a] Average % control of 5 monocot weeds at 4800 g ha^{-1}. [b] Average % control of 5 dicot weeds at 4800 g ha^{-1}.



24 **25** **26** **27**

Figure 4. Herbicidal Activity Model and Compounds Designed from the Model



a) MeC(=NH)NH$_2$.HCl, NaOAc, toluene, reflux, Dean Stark trap. b) MeI, K$_2$CO$_3$, acetone, reflux.

Figure 5. 6-Phenylpyrimidinone Preparation

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Six Membered Heterocycle Synthesis and SAR

6-Phenylpyrimidinone **25** was prepared in 2 steps (Figure 5). Reaction of acetamidine hydrochloride with β-ketoester **19** (*8*) afforded pyrimidinone **28** which was methylated under basic conditions to afford **25** as the major product This compound had bleaching activity in the greenhouse, although it was 2-4× less active than **1**. The results of a limited SAR study are shown in Table II and were consistent with our expectations based on the SAR observed in the triazolinone series (*9*).

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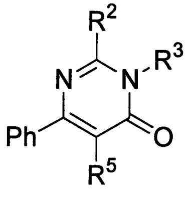
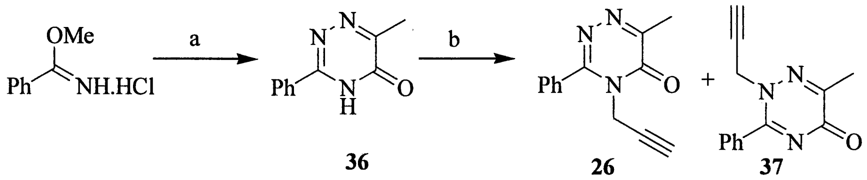
Table II. Preemergence Herbicidal Activity of 6-Phenylpyrimidinones



Cmpd	*R²*	*R³*	*R⁵*	*AM*[a]	*AD*[b]
25	Me	Me	$CH_2C{\equiv}CH$	82	79
29	H	Me	$CH_2C{\equiv}CH$	39	38
30	n-Pr	Me	$CH_2C{\equiv}CH$	81	66
31	Me	$CH_2C{\equiv}CH$	$CH_2C{\equiv}CH$	72	78
32	$-CH_2CH_2CH_2CH_2-$		$CH_2C{\equiv}CH$	79	64
33	$-SCH_2CH_2-$		$CH_2C{\equiv}CH$	63	10
34	Me	Me	H	0	0
35	Me	Me	Br	2	0

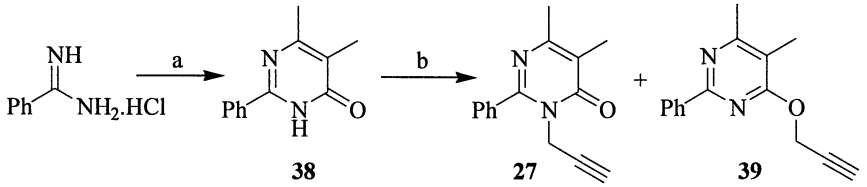
[a] Average % control of 5 monocot weeds at 4800 g ha^{-1}. [b] Average % control of 5 dicot weeds at 4800 g ha^{-1}.

The route used to prepare 1,2,4-triazin-5-one **26** is shown in Figure 6. Treatment of methyl benzimidate hydrochloride with hydrazine followed by methyl pyruvate afforded triazinone intermediate **36** which was alkylated with propargyl bromide (*10*). The major product was the undesired regioisomer **37**; however the desired product **26** was isolated in 2% yield. This compound caused only very slight bleaching on new leaf tissue when applied preemergence and was not pursued further.



a) i. NaOMe, MeOH; ii. N_2H_4; iii. $MeCOCO_2Me$. b) $BrCH_2C{\equiv}CH$, NaOMe, MeOH

Figure 6. 1,2,4-Triazin-5-one Preparation



a) $MeCOCHMeCO_2Me$, NaOAc, xylenes, reflux, Dean Stark trap. b) $BrCH_2C{\equiv}CH$, K_2CO_3, acetone, reflux.

Figure 7. 2-Phenylpyrimidinone Preparation

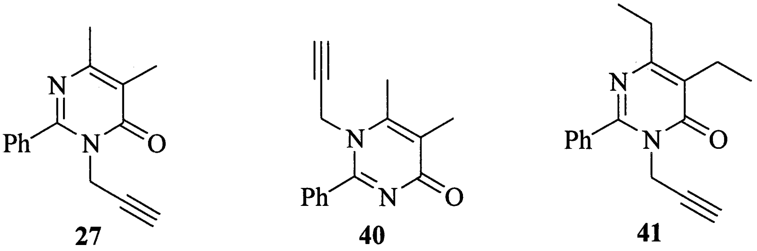


Figure 8. N-Propargylpyrimidinone Regioisomers

The route used to prepare 2-phenylpyrimidinone **27** is shown in Figure 7. Reaction of benzamidine hydrochloride with methyl acetoacetate afforded **38** (*8*). Propargylation of this intermediate under basic conditions proceeded in 90% yield to afford a 10:1 mixture of the undesired O-propargyl compound **39** and the desired N-propargyl product **27**. These isomers were readily separated by flash chromatography. The preemergence herbicidal activity of **27** in the greenhouse was equal to that of the original lead compound **1**. However, **27** appeared to offer an improved starting point for analog synthesis. The two sp^2

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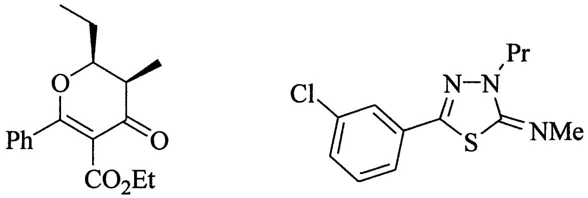
carbons C^5 and C^6 allow greater flexibility in the types of substituents that can be stably appended than does N^2 in the triazolinone ring. For example a chlorine substituent at either C^5 or C^6 of the pyrimidinone ring should be reasonably chemically stable whereas an N^2-chlorotriazolinone would be chemically reactive. Furthermore, the two positions offer greater ability to tailor the substituents to fill the binding pocket occupied by the *t*-butyl group in **1**.

Given our interest in **27** as a new lead it was important to establish the regiochemistry of N-propargylation and be certain that the propargyl group was indeed attached at N^3 and not to the N^1 position (**40**, Figure 8). Literature precedent favored structure **27** since alkylation at N^3 is observed more frequently than at N^1 (*11*). The stretch of the carbonyl in the IR spectrum was also more consistent with structure **27** (*12*). No NOE could be detected between the propargyl methylene and the C^6 methyl group, again favoring structure **27**. Ultimately all doubt was removed when an X-ray structure was obtained on **41**, the 5,6-diethyl analog of **27**.

At the time this work was in progress we were aware of several other herbicidal chemotypes that function by inhibiting zeta carotene desaturase (*13*). Dihydropyrone **42** (*14*) and iminothiadiazole **43** (*15*) shown in Figure 9 were of particular interest since, like our compounds, they are both phenyl-substituted heterocyclic systems. In the greenhouse **1** and **27** had comparable activity to **42** and were superior to **43** (Table III). Based on the hypothesis that these compounds may occupy the same binding site, we synthesized a number of compounds as hybrids of our compounds and the literature compounds. For example isoxazolidinone **23** (Figure 10) can be considered to be a hybrid of **16** and **42**. Similarly **44** and **10** can be considered to be hybrids of **1** and **43**. None of the hybrid compounds prepared had significant greenhouse activity.



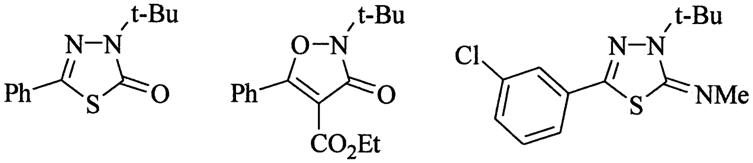
42 **43**

Figure 9. Zeta Carotene Desaturase Inhibitors

Table III. Comparison with Herbicidal Activity of Known Zeta-Carotene Desaturase Inhibitors

Cmpd	*Structure Type*	*AM*[a]	*AD*[b]
		(600 g ha^{-1})	
1	Triazolinone	67	72
27	Pyrimidinone	59	75
42	Dihydropyrone	62	65
43	Iminothiadiazole	44	23

[a] AM = average % control of 8 monocot weeds preemergence. [b] AD = average % control of 12 dicot weeds preemergence.



10 **23** **44**

Figure 10. Hybrid Compounds

Conclusions

Systematic replacement of the triazolinone ring of **1** with other heterocycles led to the discovery of three new herbicidal series of which isoxazolidinone **16**, 6-phenylpyrimidinone **25** and 2-phenylpyrimidinone **27** were the lead compounds. The last of these had comparable activity to **1** and offered increased flexibility for analog synthesis.

Acknowledgments

The success of this project would not have been possible without the dedicated efforts of many of our coworkers at Rohm and Haas. Scale Up Chemistry: Ronald P. Owen, Judith A.H. Schilling; Greenhouse Biology: Manuel V. Nunez; Molecular Modelling; Ted T. Fujimoto; Biochemistry: Ernest L. Burdge, Christine A. Cayer; Management: Horst O. Bayer.

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Chapter 6

Synthesis of Herbicidal 2-Aryl-4-(3*H*)-pyrimidinones

Colin M. Tice[1], Lois M. Bryman[1], Renee C. Roemmele[1], Edward C. Taylor[2], Ping Zhou[2], Janusz Jurczak[3], and Artur Jezewski[3]

[1]**Rohm and Haas Company, 727 Norristown Road, Spring House, PA 19477–0904**
[2]**Department of Chemistry, Princeton University, Princeton, NJ 08544–1009**
[3]**Institute of Organic Chemistry, Polish Academy of Sciences, 01–224 Warsaw, Poland**

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5,6-Dimethyl-2-phenyl-3-propargyl-4(3H)-pyrimidinone **1** possesses lead level herbicidal activity. Several hundred analogs were synthesized in an effort to identify compounds with higher levels of activity. In the course of this work four different synthetic routes were employed to produce five analogs for field testing. The most promising analog, 5-ethyl-2-phenyl-3-propargyl-6-(trifluoromethyl)-4(3H)-pyrimidinone **16**, was extensively field tested in winter wheat.

2-Phenylpyrimidinone RH 100186 (**1**, Figure 1) (*1*) was discovered during exploration of the heterocyclic SAR of 5-phenyltriazolinone RH 88488 **2**. Like its predecessor, **1** was a bleaching herbicide with broad spectrum preemergence activity and caused the accumulation of phytoene, phytofluene and zeta carotene in treated tissue (*2*).

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

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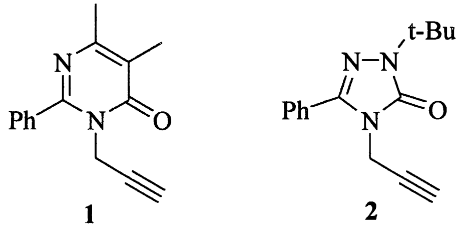
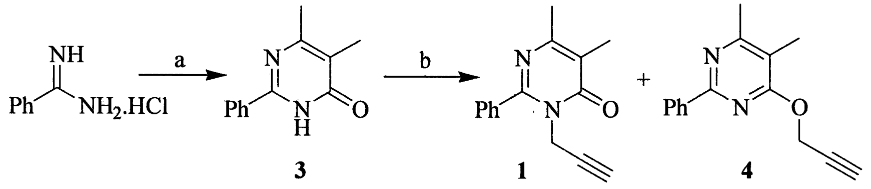


1 **2**

Figure 1. Lead Compounds



3 **1** **4**

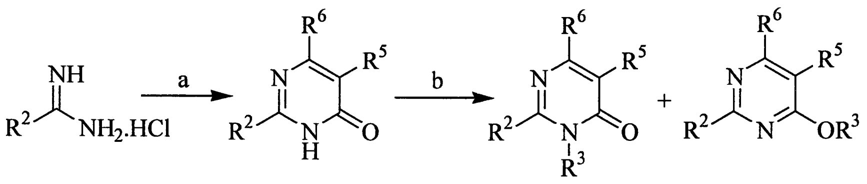
a) $MeCOCHMeCO_2Me$, NaOAc, xylenes, reflux, Dean Stark trap. b) $BrCH_2C{\equiv}CH$, K_2CO_3, acetone, reflux.

Figure 2. Original Synthesis of **1**

Alkylation Route

The original synthesis of **1** is depicted in Figure 2. Benzamidine was reacted with methyl acetoacetate in refluxing xylenes to afford pyrimidinone intermediate **3** (*3*). Propargylation of **3** proceeded in high yield under the conditions shown but the desired N-propargyl compound **1** comprised only 10% of the crude product; O-propargyl compound **4** was the predominant product. Despite the poor regioselectivity in the propargylation step, **1** and **4** were readily separated by flash chromatography and sufficient material could be obtained for greenhouse testing. The first analogs of **1** were also prepared using these conditions (Figure 3). Non-commercially available amidines **5** were prepared from the corresponding nitriles $R^2C{\equiv}N$ *via* the imidate $R^2C(OMe){=}NH$. When R^2 was an electron donating group *e.g.* 3-methylphenyl, the imidate was prepared from the nitrile using methanol saturated with HCl gas (*4*). When R^2 was an electron withdrawing group *e.g.* pyridyl, the imidate could be prepared by the action of catalytic sodium methoxide on the nitrile (*5*). Acylation of the dianions of malonate monoester $R^5CH(CO_2H)CO_2Et$ with acid chlorides

R^6COCl was employed for the synthesis of many non-commercially available β-ketoesters $R^6COCHR^5CO_2Et$ (*6*).



5 **6** **7** **8**

a) $R^6COCHR^5CO_2Et$, NaOAc, xylenes, reflux, Dean Stark trap. b) R^3X, K_2CO_3, acetone, reflux.

Figure 3. Initial Analog Synthesis Route

As the analog synthesis program proceeded, the preference for O-alkylation of the 2-arylpyrimidinones **6** became increasingly problematic. Examination of the literature revealed that, in contrast to our experience, alkylation of pyrimidin-4(3H)-ones usually occurs preferentially at N^3 (*7*). We speculated that the anion of the 2-aryl-4(3H)-pyrimidinones adopts a conformation in which the two rings are coplanar and the ortho hydrogen of the aryl ring blocks the approach of the alkylating agent to N^3 (**9**, Figure 4) thus favoring O-alkylation. Support for this hypothesis comes from the propargylation of 2-(2-fluorophenyl)-4(3H)-pyrimidinone **10** in which N^3 is the favored site of propargylation. Because of the presence of an ortho substituent, the anion of **10** is expected to adopt a conformation in which the fluorophenyl and pyrimidinone rings are no longer coplanar and N^3 becomes accessible to the alkylating agent. Interestingly, methoxymethylation of **9** under acidic condition ($MeOCH_2OMe$, P_2O_5) (*8*) afforded predominantly the N^3-methoxymethyl product.

Since the developing structure activity favored compounds with R^3 = $CH_2C{\equiv}CH$ and R^6 = CF_3, efforts to improve the regioselectivity of the alkylation step focused on propargylation of 2-phenyl-6-(trifluoromethyl)-4(3H)-pyrimidinone **11** using the commercially available propargyl bromide. A wide variety of bases and solvents was explored. Some selected results are shown in Table I. The best conditions found employed sodium methoxide as base and methanol as solvent (*9*) and afforded a 1:2 ratio of the desired **12** to the undesired **13**. The improved product ratio came at the expense of incomplete conversion of **11** which could not be removed by extraction into aqueous NaOH, presumably because its sodium salt is insoluble in water. In addition **11** was difficult to separate from **12** by chromatography. Nonetheless these

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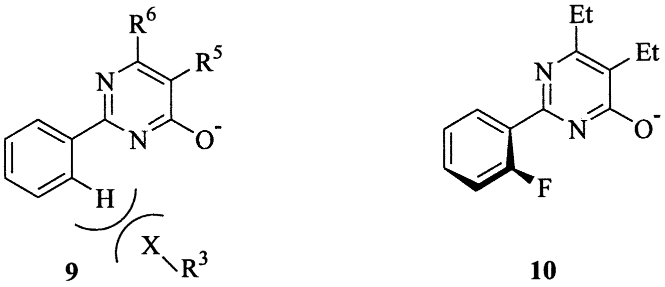
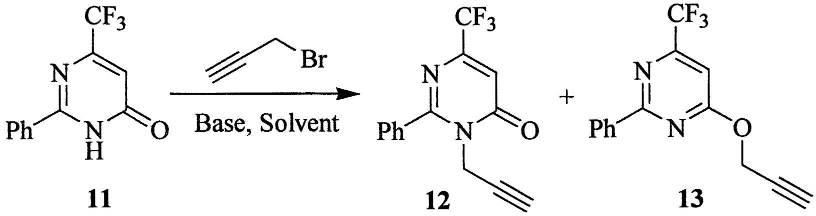
conditions did allow preparation of 100 g quantities of analogs **14** and **15** (Figure 5) for field testing.



9 **10**

Figure 4. Effect of Conformation on Alkylation Regioselectivity

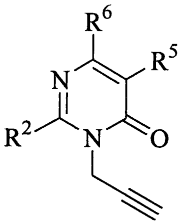
Table I. Propargylation of 2-phenyl-6-(trifluoromethyl)-4(3H)-pyrimidinone



11 **12** **13**

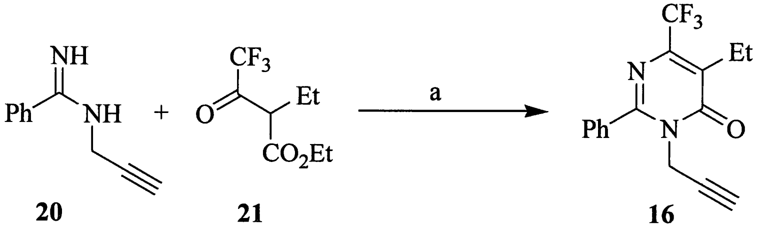
Base	*Solvent*	*N:O*[a]	*Comments*
K_2CO_3	Acetone	1:12	90% conversion
BuLi	PhMe		No propargylation
KOH	H_2O-DMSO	1:7	
KH	MeOH	1:3	75% conversion
NaOMe	MeOH	1:2	85% conversion
KH	t-BuOH	1:1.5	Byproducts

[a] Ratio was determined by ^1H NMR and GC of the crude product



14 $R^2 = Ph, R^5 = Me, R^6 = Et$
15 $R^2 = Ph, R^5 = Et, R^6 = Et$
16 $R^2 = Ph, R^5 = Et, R^6 = CF_3$
17 R^2 = 2,6-diCl-4-pyridyl, $R^5 = Et, R^6 = Et$
18 R^2 = 2,6-diCl-4-pyridyl, $R^5 = Et, R^6 = Me$
19 R^2 = 2,6-diCl-4-pyridyl, $R^5 = OMe, R^6 = Me$

Figure 5. Field Test Candidates



a) CH_2Cl_2, reflux, 3 d.

Figure 6. Direct Preparation of 6-Trifluoromethyl-4(3H)-pyrimidinones

Direct Synthesis from N-propargylamidines

Further analog synthesis led to the emergence of RH 111965 (**16**, Figure 5) as the most promising compound in the series and 1 kg of this compound was desired for field testing. It became apparent that the existing route was not feasible to produce this quantity of **16** and we sought an alternate approach. Direct reaction of N-propargylbenzamidine **20** with β-ketoester **21** would circumvent the troublesome propargylation reaction (Figure 6). However, few examples of the reaction of N-monosubstituted amidines with β-ketoesters exist. Sitte and Paul (*10*) reported that the reaction fails when the β-ketoester bears an alkyl substituent at the α-position, the substitution pattern that is present in **21**. In addition **20** is prone to decomposition on heating (*11*). Nonetheless, we reasoned that electrophilicity of the trifluoromethyl ketone might allow the reaction to proceed and were indeed able to optimize this reaction to allow preparation of **16** in the requisite quantities (*12*).

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Compound **16** was widely field tested for use in several potential markets. Very little loss of activity occurred in going from the greenhouse to the field. Early postemergence application to winter wheat in Europe appeared to be the most promising market. The compound was safe to winter wheat at 150 g ha^{-1}. It gave excellent control of the important broadleaf weeds, viola, mustards, brassica, crucifera and poppies at this rate but incomplete control of veronica and galium. Control of blackgrass and ryegrass was good at 150 g ha^{-1} but a mixing partner was required to attain complete control. Isoproturon was explored in this role. Increasing the application rate of **16** to 300 g ha^{-1} afforded complete control of many key weeds but with an insufficient margin of safety to wheat. Furthermore, preliminary estimates of manufacturing cost suggested that application rates above 150 g ha^{-1} were unlikely to be economically feasible. Nonetheless the field performance of **16** was sufficiently promising to encourage us to continue our synthesis program in search of superior analogs.

Triflate Route

Around this time, the commercial availability of 2,6-dichloropyridine-4-carboxamidine (**23**, Figure 7) prompted us to synthesize **17** (Figure 5) using the alkylation route (Figure 3). Compound **17** showed good herbicidal activity and was the first analog in the series to be safe to soybeans. The activity of **17** was somewhat surprising since analogs **7** (Figure 3) with R^2 = 3,5-dichlorophenyl had diminished activity compared to R^2 = phenyl and compounds with R^2 = 4-pyridyl were almost devoid of activity at the highest rate tested. It also proved fortuitous that we prepared **17** before **22** since the latter compound had much less activity, indicating that SAR trends at R^5 and R^6 differ depending on whether R^2 = Ph or 2,6-dichloro-4-pyridyl (Table II). In any event, the activity of **17** spawned a new area of analog synthesis in which various heteroaromatic moieties, especially halopyridyl groups, were installed at R^2. Compounds **18** and **19** (Figure 5) also emerged from this area of synthesis as candidates for field testing in addition to **17**. Interestingly, the soybean selectivity observed with **17**, was unique to this analog.

We were obliged to seek a new route to prepare 50 g of **17** for initial field testing. The alkylation route was not feasible because the electron withdrawing dichloropyridyl substituent engenders a very unfavorable ratio of N:O propargylation even with the best conditions and the presence of an ethyl group at R^6 ruled out the direct synthesis from an N-propargylamidine. We began to investigate routes in which either R^5 or R^6 is appended to a preformed pyrimidinone ring.

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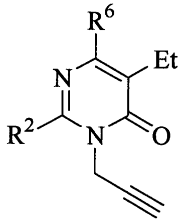
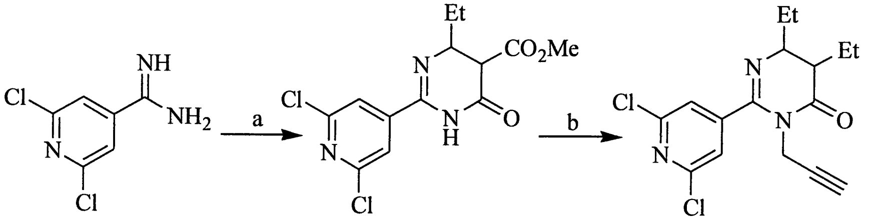
Table II. Structure Activity of Dichloropyridyl and Phenyl Analogs[a]



Cmpd	*R²*	*R⁶*	*AM[b]*	*AD[c]*
			150 g ha⁻¹	
15	Ph	Et	74	28
16	Ph	CF_3	81	47
17	2,6-diCl-4-pyridyl	Et	77	25
22	2,6-diCl-4-pyridyl	CF_3	41	10

[a] R groups refer to 7 in Figure 3. [b] % control preemergence of 8 monocot weeds [c] % control preemergence of 7 dicot weeds

Dihydropyrimidinone **24** (Figure 7) was prepared and the ethyl group at R^5 was added by alkylation of its dianion with ethyl iodide. A second alkylation installed the propargyl group on N^3. Decarboxylation afforded **25**, the 5,6-dihydro analog of **17**. All attempts to oxidize **25** to **17** failed. Dihydropyrimidinones such as **25** are themselves herbicidal (*13*).



23 **24** **25**

a) $EtCH{=}C(CO_2Me)_2$. b) i. EtI, KOt-Bu (2 eq), DMF; ii. NaH, DMF; iii. $HC{\equiv}CCH_2Br$; iv. LiI, pyridine.

Figure 7. Dihydropyrimidinone Route

Triflate **27** (Figure 8) attracted our attention as a potentially versatile intermediate for installation of a variety of groups at R^6 using organometallic reagents (*14*). Treatment of N-propargylamidine **26** with sodium bis(trimethylsilyl)amide at low temperature, followed by ethylmalonyl dichloride, afforded a 6-hydroxypyrimidinone which was reacted with triflic

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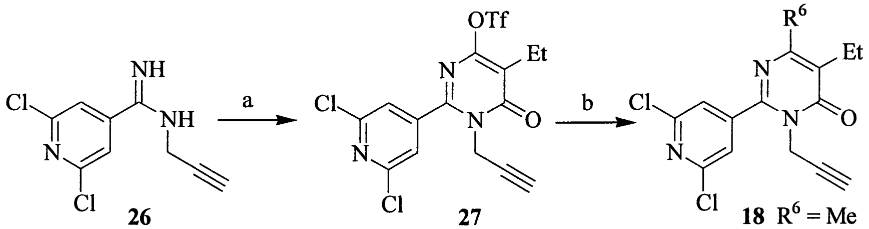
anhydride to afford **27**. Reaction of **27** with $Me_2CuCNLi_2$ afforded a 7:1 mixture of **18** and reduction product **28** (*15*). This route was used to produce 50 g of **18** for field testing. Unfortunately, treatment of **27** with $Et_2CuCNLi_2$ gave mostly reduction product **28**, rather than the desired 6-ethylpyrimidinone **17**..

The utility of **27** in palladium catalyzed chemistry such as the Stille reaction was compromised by the reactivity of the terminal acetylene, so trimethylsilyl protected analog **29** was prepared and used to prepare several hitherto inaccessible analogs. For example, reaction of **29** with vinyltributyltin and allyltributyltin afforded **30** and **31** respectively after desilylation (Figure 9) (*16*). However, despite numerous attempts using a variety ethylorganometallics, we were unable to efficiently introduce an ethyl group into **29** and were not able to obtain **17** by this route. Furthermore, initial attempts to prepare 5-methoxypyrimidinone **19** (Figure 5) using a 5-methoxy-6-trifluoromethanesulfonyloxy-4(3H)-pyrimidinone did not give promising results.



26 **27**

18 $R^6 = Me$

28 $R^6 = H$

a) i. NaHMDS, THF, -70°C; ii. $EtCH(COCl)_2$; iii. Tf_2O, 2,6-lutidine, CH_2Cl_2.
b) $Me_2CuCNLi_2$, THF, -70°C.

Figure 8. Triflate Route

High Pressure Route

It occurred to us that the direct reaction of an amidine with a β-ketoester might be feasible under high pressure conditions (*17*) even without the presence of a trifluoromethyl group. Thus, reaction of amidine **26** with an α-methoxy-β-ketoester **31** in absolute ethanol at 10 kbar proceeded in 43% yield to afford **19** (Figure 10). This route was used to produce 50 g of **19** for field testing and the chemistry was also demonstrated to be applicable to **18**.

The field test results with the dichloropyridyl compounds **18** and **19** were generally disappointing. Unlike **16**, these compounds were significantly less active in the field than the greenhouse.

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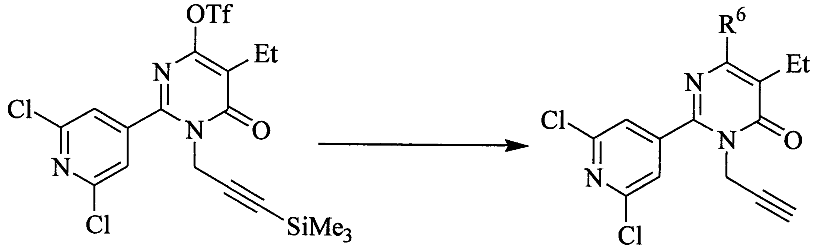


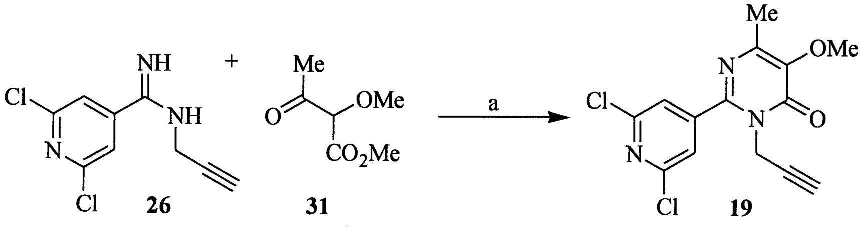
29

30 $R^6 = CH{=}CH_2$

31 $R^6 = CH_2CH{=}CH_2$

a) i. Bu_3SnR^6, LiCl, tri(2-furyl)phosphine, Pd_2dba_3, NMP, 25°C, 24-48 h; ii. KF, HOAc, MeOH.

Figure 9. Palladium Catalyzed Reactions on Triflate intermediate **29**



26 **31** **19**

a) Et_3N, EtOH, 10 kbar, 25°C, 65 h.

Figure 10. High Pressure Route

Conclusions

Four different synthetic routes were developed to allow initial scale up of five 2-aryl-3-propargyl-4(3H)-pyrimidinones for field testing. RH 111965 (**16**, Figure 5) had the most promising field performance and was tested extensively in winter wheat. Ultimately, however, it did not meet our criteria for development.

Acknowledgments

The success of this project would not have been possible without the dedicated efforts of many of our coworkers at Rohm and Haas. Scale Up Chemistry: William J. Zabrodski, William C. Thompson; Greenhouse Biology: Manuel V. Nunez, Vincent A. Musco, James D. Fisher, Mark D. Swain, William DenBleyker; Molecular Modelling: Ted T. Fujimoto, Charles H. Reynolds; Biochemistry: Ernest L. Burdge, Christine A. Cayer; Field Testing: Harlow L. Warner; Management: Horst O. Bayer, Zev Lidert.

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Chapter 7

Synthesis and Structure–Activity Relationships of Benzoheterocyclic and Pyridoheterocyclic Protoporphyrinogen Oxidase Herbicides

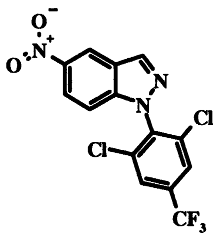
D. R. James[1], R. A. Felix[1], W. J. Michaely[2], C. J. Mathews[3], D. R. Baker[4], C. G. Knudsen[1], F. M. Pallos[5], J. M. Gerdes[6], S. Fitzjohn[3], T. H. Cromartie[3], S. W. Howard[3], D. P. Dagarin[3], and M. Broadhurst[3]

[1]Cambridge Discovery Chemistry, Inc., 1391 South 47th Street, Richmond, CA 94804
[2]Chemistry Department, University of San Francisco, 2130 Fulton Street, San Francisco, CA 94117
[3]Zeneca Agrochemicals, Jealott's Hill Research Station, Bracknell RG12 6EY, United Kingdom
[4]Consultant, Chemistry and Chemical Health/Safety, 15 Muth Drive, Orinda, CA 94563
[5]135 Twin Peaks Drive, Walnut Creek, CA 94595
[6]Chemistry Department, Central Washington University, Ellensburg, WA 98926

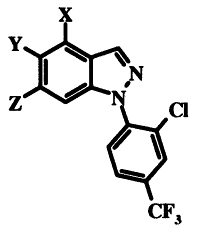
Work was done at Zeneca Ag Products, 1200 South 47th Street, Richmond, CA 94804.

The Zeneca insecticide discovery program provided a lead herbicide candidate based on a benzopyrazole structure **1**. Biochemical assays showed this lead to be a novel protoporpyrinogen oxidase (Protox) inhibitor. A synthesis program to optimize the lead activity lead to the discovery of a variety of novel

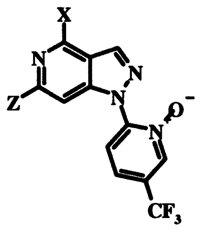
heterocyclic scaffolds with protoporphyrinogen oxidase (PPGO)-based herbicide activity, e.g. **2** and **3**. Chemistry was developed to produce polysubstituted fused heterocycles enabling the preparation of very active (1-5 gram/Hectare) pre-emergent (PES) and post emergent (POSTEM) herbicides for use in soya and corn. The resulting synthetic schemes and structure-activity relationships are presented.



1



2



3

A decade ago the mechanism of action of diphenyl ether (DPE) herbicides was definitively established by two separate research teams (*1,2*). The newly established target enzyme of numerous DPE herbicides, protoporphyrinogen oxidase (Protox), immediately became the subject of intense scrutiny throughout the agricultural industry as corporate compound collections were rescreened against an *in vitro* PPGO assay. We had previously identified several chemical entities from our insecticide program that displayed DPE-type herbicide symptoms, i.e., pre- and early-postemergence control of grasses and small seeded, broadleaved weeds following a rapid onset of browning of the foliage. In addition, these chemicals displayed a degree of safety to soya, a common observation with DPE herbicides. These few compounds, along with a large number of other entities, were screened in the newly established protoporphyrinogen oxidase assay using maize etioplasts. In this assay, one of these insecticide candidates, compound **1**, gave an IC_{50} = 7 nM indicating that PPGO inhibition is most likely the mechanism of action of this class of compounds; for comparison, the Zeneca soya herbicide fomesafen **4** gave an IC_{50} = 29 nM in the same assay.

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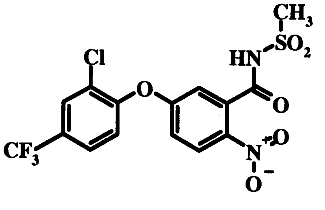
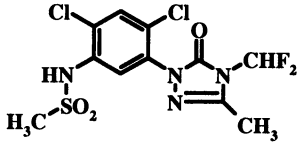


4
fomesafen



5
sulfentrazone

Numerous papers have been published describing the structural requirements of both the diphenyl ether and imide types of PPGO inhibitor (*3-5*). Recently, sulfentrazone **5** was described as belonging to the 2,4,5-trisubstitution (imide) class of herbicide (*6*). It seemed likely to us that the lead compound **1** represented an example of the diphenyl ether class with a 2,4,6-substitution pattern on the phenyl ring and that only a limited set of replacement substituents, based on literature precedent, would probably be acceptable on this "A" ring (Figure 1).

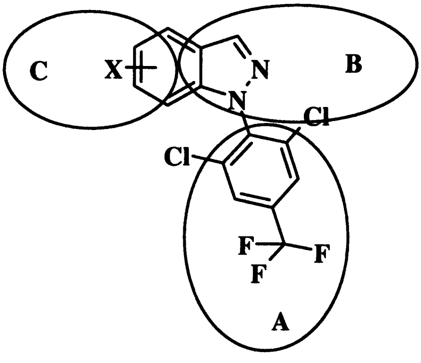


Figure 1. Structure modification domains.

With this in mind, a lead optimization plan was established whereby chemist teams pursued each of three domains labeled A, B and C in Figure 1.

General Structural Assumptions

It was demonstrated that diphenyl ether herbicides are competitive with the natural substrate protoporphyrinogen IX in their inhibition of PPGO(*7-8*).

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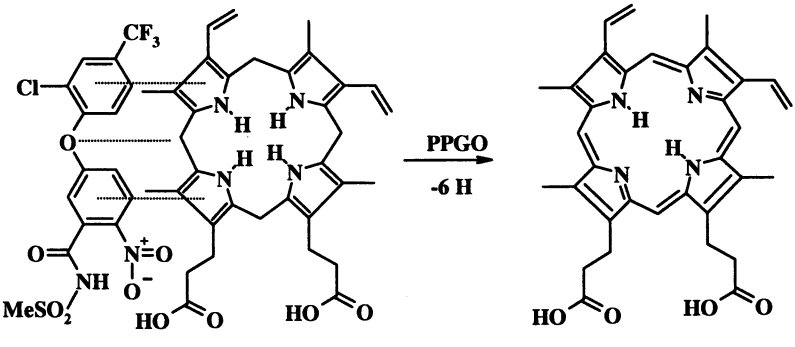

reflex **protoporphyrinogen IX** **protoporphyrin IX**

Figure 2. Herbicide overlay on natural substrate.

We assumed that diphenyl ethers as well as our new lead indazole mimic half of the porphyrin ring system whereby the torsion angles of the two aromatic rings match up with two pyrrole rings from PP-IX, as illustrated in Figure 2 To complicate the analysis we conjectured that the herbicide might mimic one of the 2-electron oxidation intermediates on the way to the fully oxidized protoporphyrin IX. If the herbicide mimics an intermediate stage in this integrated oxidation process then it is likely that the enzyme kinetics would imply a competitive inhibition of the reduced substrate. To this point the LUMOs of the substrate and intermediates differing by 2 electrons were calculated and compared to the LUMO energies of various PPGO herbicides, including the newly discovered Indazole. The new lead clearly fit well with the later observation of Akagi and Sakashita that PPGO herbicides contain a very low LUMO energy, implying a charge transfer phenomenon at the active site of PPGO (*9*). Interestingly, the LUMOs of PP-IX and its oxidation intermediates confirmed that the intermediates might prove more relevant to the binding of PPGO herbicides than the reduced substrate (Table I). A second supposition in our model was that *ortho*-substitution was necessary on the A-ring in order to force that ring out of planarity with the attached aromatic B-ring scaffold. This aspect of PPGO herbicide design is implicit in the discussions of S. Duke and G.Durst (*4-5*). The historic diversity in the substitution pattern on the B-ring scaffold of diphenyl ether herbicides proved to be the best opportunity for fine tuning the biological activity of our indazole-class of herbicides.

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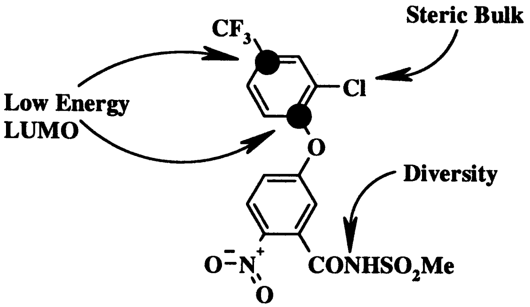
Table I. Structural Considerations for Herbicide Acitivity



Molecule	*LUMO eV*
Reflex	-1.89
Acifluorfen	-1.62
5-Nitroindazole	-1.54
Protogen-6	-1.39
Protogen-4	-1.31
Chlorophthalim (imide)	-1.23
Protogen-2	-1.2
RH1422 (carbamate)	-0.78
Protogen	0.8

With these molecular considerations in mind we sought to optimize three distinct areas of the indazole lead concomitantly (Figure 1).

A-ring attachment on Heterocyclic scaffold

The substituted phenyl rings were generally attached to the heterocyclic scaffold by a nucleophilic arylation reaction. Where multiple nucleophilic sites were present as in the indazole scaffold, the reaction generally gave the desired N-1 product in sufficient yield after separation and purification. In some instances, a different route was used to provide unambiguous preparation of a single positional isomer (Figure 3).

In other instances, as with benzotriazoles, N-1 aryl derivatives were prepared selectively by addition of the A-ring prior to heterocyclic ring formation (Figure 4).

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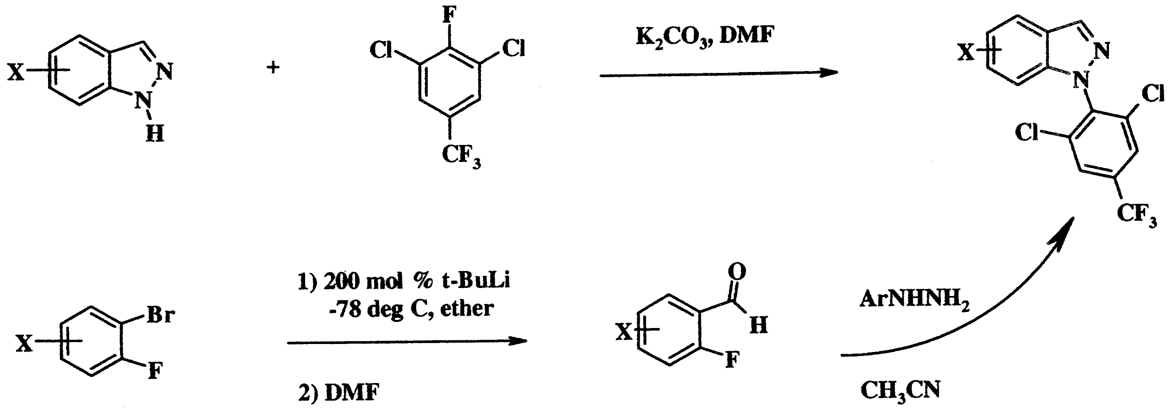
X
N
N
H
+
F
Cl
Cl
CF3
K2CO3, DMF
X
N
N
Cl
Cl
CF3
X
Br
F
1) 200 mol % t-BuLi
-78 deg C, ether
2) DMF
X
O
H
F
ArNHNH2
CH3CN

Figure 3. Primary routes to substituted indazoles.

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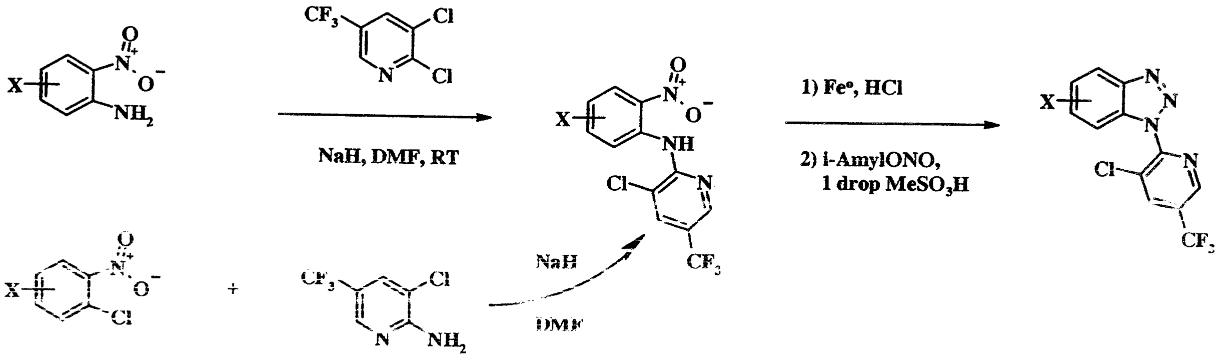
NaH, DMF, RT
1) Fe°, HCl
2) i-AmylONO,
1 drop MeSO3H
NaH
DMF
+

Figure 4. Primary routes to substituted benzotriazoles.

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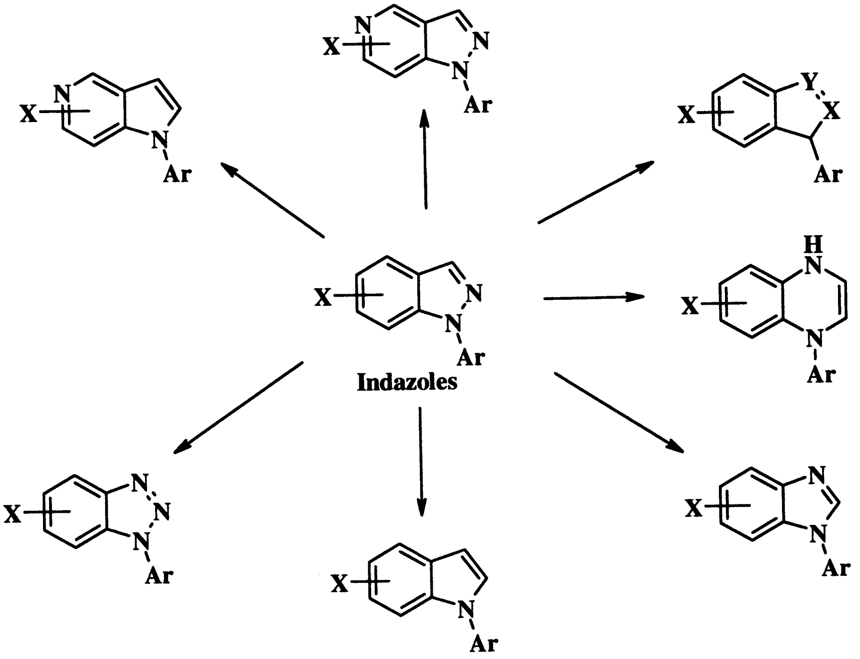

Figure 5. Scaffold replacements.

B-Ring Scaffolds and substituents

A wide variety of B-ring scaffolds were prepared and modified by addition of the usual A-ring and accompanying substituents. Figure 5 shows the main modifications attempted, most of which gave compounds with herbicidal activity. These ring systems were prepared by published procedures.

Substituted Indoles were prepared from *ortho*-nitrotoluenes (Figure 6).

Indazoles which were not commercially available were likewise prepared from *ortho*-nitrotoluenes using a diazotization procedure for producing the pyrazole ring (Figure 7).

Substituted benzotriazoles were generally prepared from the corresponding *ortho*-nitroanilines by diazotization and functionalization of the resultant heterocycle (Figure 8).

Pyrazolopyridines and pyrrolopyridines offer unusual scaffolds for herbicide construction. Both were prepared by routes analogous to those in Figures 6 and 7 (Figure 9).

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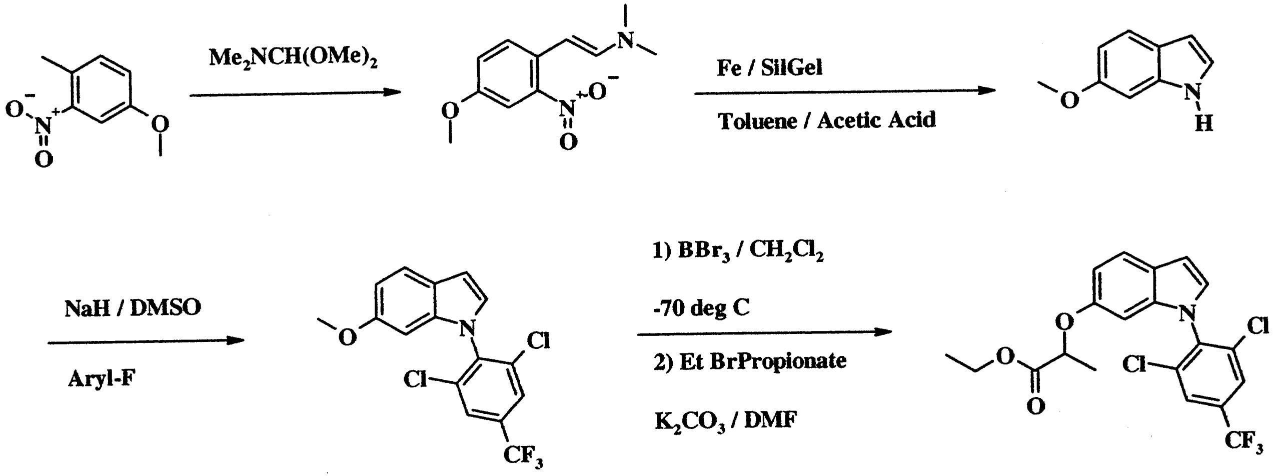
Me$_2$NCH(OMe)$_2$
Fe / SilGel
Toluene / Acetic Acid
NaH / DMSO
Aryl-F
1) BBr$_3$ / CH$_2$Cl$_2$
-70 deg C
2) Et BrPropionate
K$_2$CO$_3$ / DMF
O
N
H
Cl
CF$_3$

Figure 6. Primary route to indoles.

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
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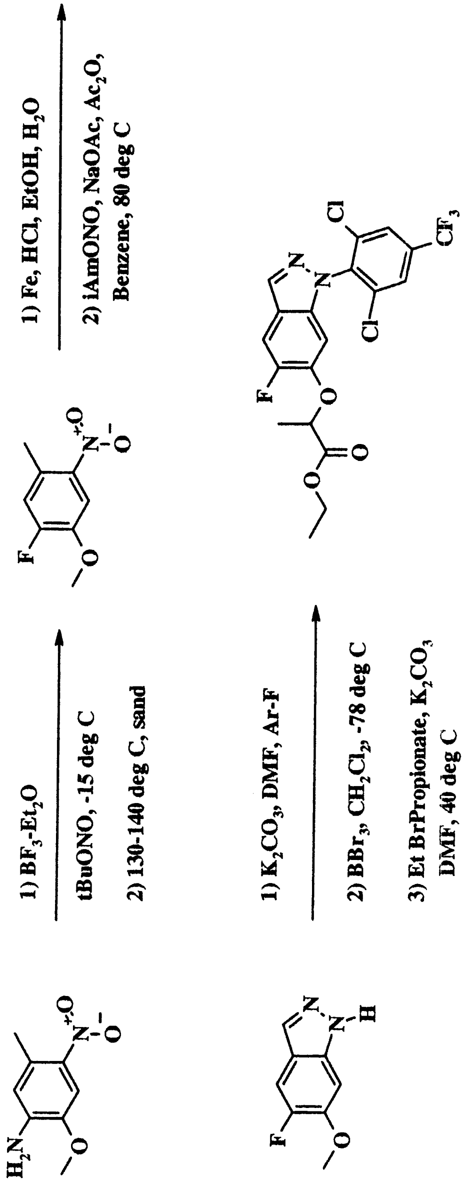
H$_2$N
1) BF$_3$-Et$_2$O
tBuONO, -15 deg C
2) 130-140 deg C, sand
F
1) Fe, HCl, EtOH, H$_2$O
2) iAmONO, NaOAc, Ac$_2$O, Benzene, 80 deg C
1) K$_2$CO$_3$, DMF, Ar-F
2) BBr$_3$, CH$_2$Cl$_2$, -78 deg C
3) Et BrPropionate, K$_2$CO$_3$ DMF, 40 deg C
Cl
CF$_3$

Figure 7. Route to polysubstituted indazoles.

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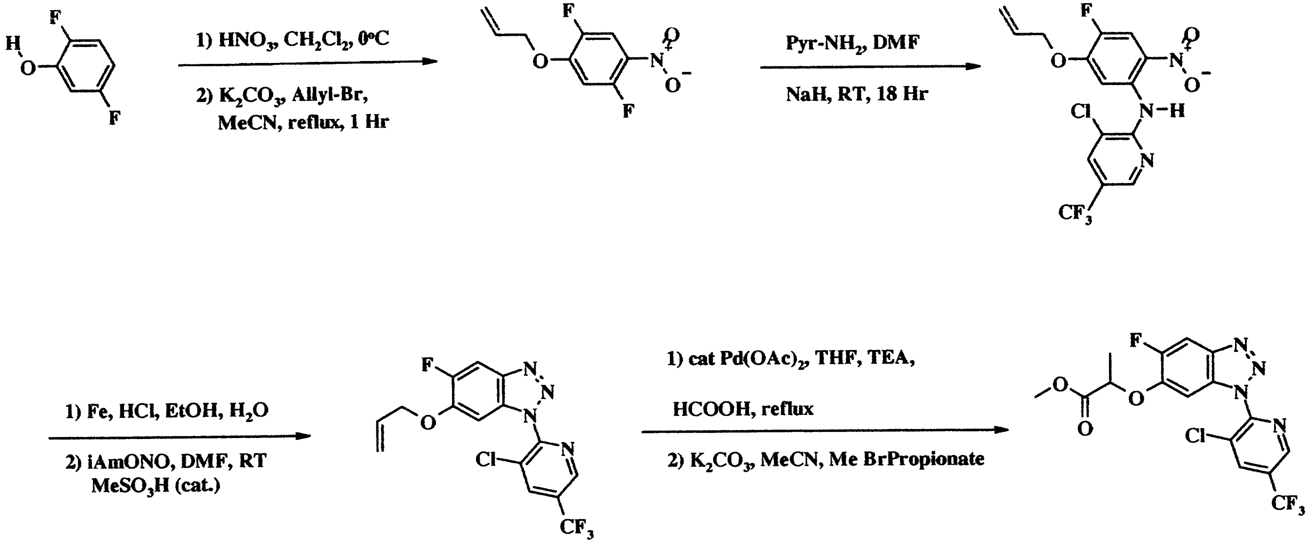
1) HNO_3, CH_2Cl_2, 0°C
2) K_2CO_3, Allyl-Br,
MeCN, reflux, 1 Hr
Pyr-NH_2, DMF
NaH, RT, 18 Hr
1) Fe, HCl, EtOH, H_2O
2) iAmONO, DMF, RT
$MeSO_3H$ (cat.)
1) cat $Pd(OAc)_2$, THF, TEA,
HCOOH, reflux
2) K_2CO_3, MeCN, Me BrPropionate

Figure 8. Route to polysubstituted benzotriazoles.

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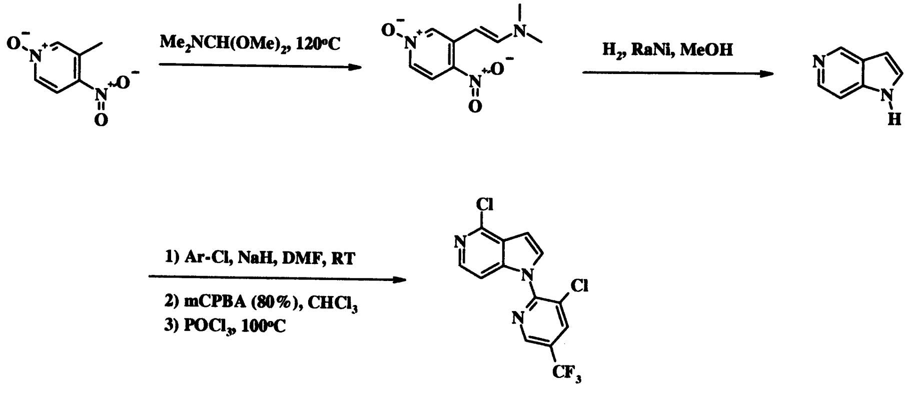
Me$_2$NCH(OMe)$_2$, 120°C
H$_2$, RaNi, MeOH
1) Ar-Cl, NaH, DMF, RT
2) mCPBA (80%), CHCl$_3$
3) POCl$_3$, 100°C
Cl
CF$_3$

Figure 9. Primary route to substituted pyrrolopyridines.

General SAR considerations

The biological activity of the many and varied structures inspired by the indazole lead compound suggest the following structure-activity relationship (Figure 10):

1) 7-Substituents prevent all biological activity!
2) Relatively small electron donors or acceptors are desirable in the 4-position.
3) Electron withdrawing groups are desirable in the 5-position.
4) Oxyacetates and oxypropionates (R+ enantiomer) are best at the 6-position.
5) Indazoles, benzotriazoles, and pyrazolopyridines are most robust scaffolds. None is superior to the others.
6) Most simple derivatives of 6-oxypropionate are also biologically active.

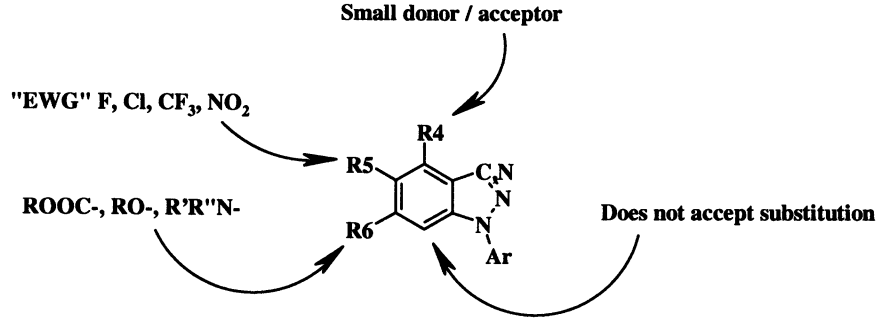
Small donor / acceptor
"EWG" F, Cl, CF$_3$, NO$_2$
ROOC-, RO-, R'R"N-
R4
R5
R6
C,N
N
N
Ar
Does not accept substitution

Figure 10. Structural requirements for herbicide acitivity.

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Chapter 8

N-Azolyl Phenoxypyrimidine Herbicides: Novel Inhibitors of Carotenoid Biosynthesis Part I

Thomas P. Selby, Joseph E. Drumm, Reed A. Coats, Frank T. Coppo, Stephen K. Gee, James V. Hay, Robert J. Pasteris, and Thomas M. Stevenson

Stine-Haskell Research Center, DuPont Crop Protection, Newark, DE 19714

Substituted 2-azolyl-4-phenoxypyrimidines of formula **1** represent a new family of highly active herbicides that act by inhibiting carotenoid biosynthesis. Azole substituents on the pyrimidine are nitrogen-linked and include pyrazole, imidazole and triazole. These compounds are active preemergence and postemergence but tend to be more active preemergence. Selectivity was observed on wheat, corn, and soybeans. There was particular interest in these compounds as cereal herbicides for preemergent and early-postemergent weed control. High field efficacy was observed, particularly on broadleaf weeds. Pyrazolylpyrimidine **1a** showed optimum activity in cereal field trials and gave excellent broadleaf weed control at rates as low as 5-10 g/ha, with good wheat safety. This paper will focus on chemistry, biology, structure-activity relationships, mode-of-action, and field activity for compounds of this herbicide class.

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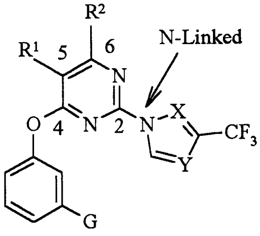
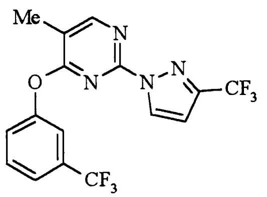
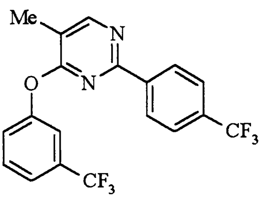
Previously, 2-aryl-4-phenoxypyrimidines such as **2** (*1*) were investigated as herbicides at American Cyanamid. More recently at DuPont, novel 2-azolyl-4-phenoxy-pyrimidines of formula **1** were also found to be highly active herbicides (*2*). Azole substituents (where X and Y are N and/or CR) on the pyrimidine core of **1** are nitrogen-linked and include pyrazole, imidazole and triazole. These compounds were shown to act by blocking carotenoid biosynthesis and were of special interest as preemergent and early post-emergent cereal herbicides for broad-spectrum weed control. Pyrazolylpyrimidine **1a** was found to provide optimum weed control at very low rates of application in field trials, with good wheat safety. In this paper, we focus on the chemistry, biology, structure-activity relationships, mode-of-action, and field activity for novel compounds of formula **1**.



1



1a



2

Chemistry

Our initial method for making 4-phenoxy-2-pyrazolylpyrimidines was non-regioselective and gave rise to isomeric products as summarized in Figure 1. Reaction of 2,4-dichloropyrimidines of formula **3** with commercially available 3-trifluoromethylpyrazole and potassium carbonate in *N,N*-dimethylformamide gave mixtures of 2-chloro-4-pyrazolylpyrimdines of formula **4** and 4-chloro-2-pyrazolylpyrimidines of formula **5** in yields of 50-60% and <10%, respectively. Proton NMR was diagnostic in the regiochemical assignments for **4** and **5** in that the R^1 proton signals on **4** versus **5** were shifted significantly downfield due to the anisotropic effect of the adjacent pyrazole substituent. Mixtures of **4** and **5** were separated by chromatography and coupled independently with 3-trifluoromethylphenol in the presence of potassium carbonate in *N,N*-dimethylformamide to afford 2-phenoxy-4-pyrazolylpyrimidines of formula **6** and 4-phenoxy-2-pyrazolylpyrimidines of formula **1b**, in yields of 60-70%. Unfortunately, this route gave rise to high yields of products **6** (with little herbicidal activity) and low yields of products **1b** (with very interesting levels of herbicidal activity).

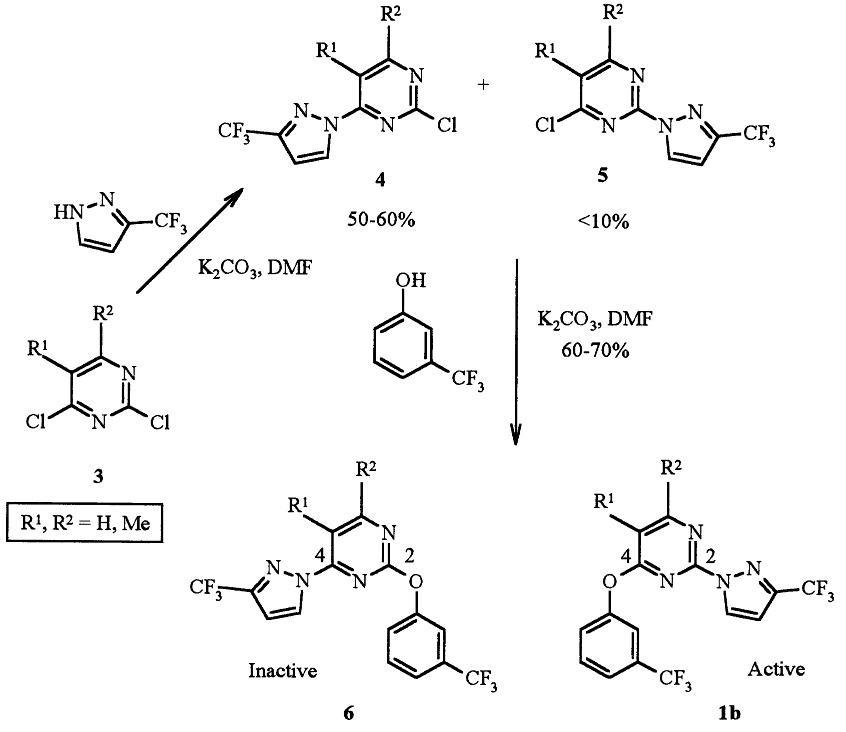


Figure 1. Non-regioselective Synthesis of Substituted Phenoxy Pyrazolylpyrimidines

An unsuccessful attempt to make a 4-phenoxy-2-pyrazolylpyrimidine as the predominant isomeric product, by reversing the order of addition of the phenol and pyrazole nucleophiles to 2,4-dichloro-5-methylpyrimidine, is shown in Figure 2. Although coupling of 2,4-dichloro-5-methyl-pyrimidine with 3-trifluoromethylphenol gave the 4-phenoxypyrimidine intermediate **7** in good yield, subsequent reaction of **7** with 3-trifluoromethylpyrazole gave rise to a mixture of products. The desired 4-phenoxy-2-pyrazolylpyrimidine **1a** was obtained in only very low yield whereas the undesired isomeric 2-phenoxy-4-pyrazolylpyrimidine **8** was actually formed as the major product along with isolation of some *bis*-pyrazolylpyrimidine **9**. Evidently, the 4-

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phenoxy substituent on 7 is an even better leaving group that the 2-chloro group, thus giving rise to the observed scrambling of product regiochemistry.

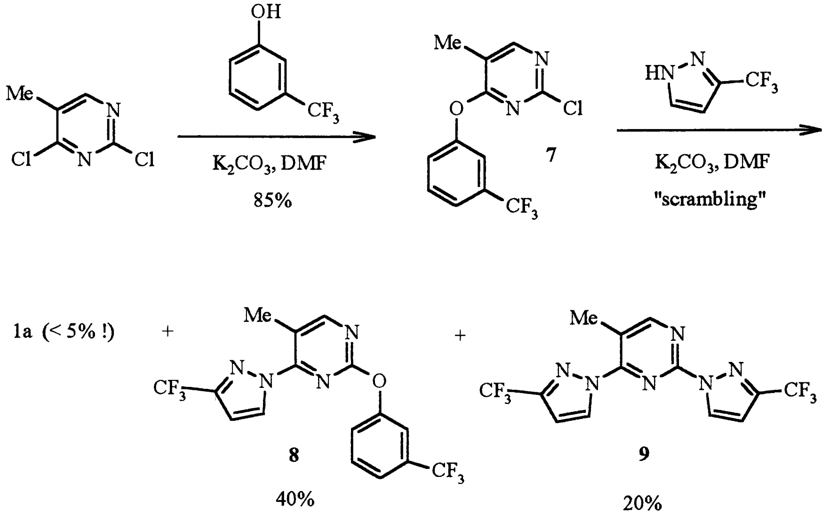

Figure 2. Unsuccessful Attempt to Prepare a 4-Phenoxy-2-pyrazolylpyrimidine as the Major Regioisomer

A successful regioselective route for making a wide-variety of 2-azolyl-4-phenoxypyrimidines in high yield was subsequently developed and is summarized in Figure 3. Reaction of 5-substituted 2,4-dichloropyrimidines of formula **10** (*3-5*) with one equivalent of sodium thiomethoxide in tetrahydrofuran gave 2-chloro-4-methylthiopyrimidines of formula **11** in good yield. Displacement of the 2-chloro group on **11** by trifluromethyl-substituted azoles of formula **12** (*6, 7*) proceeded smoothly without competitive displacement of the 4-methylthio substituent so that 2-azolyl-4-methylthiopyrimidines of formula **13** were formed in very good yields (75-80%). Oxidation of the methylthio group with *m*-CPBA gave 75-80% yields of reactive sulfones of formula **14**. Coupling sulfones of formula **14** with 3-substituted phenols of formula **15** in the presence on potassium carbonate in *N,N*-dimethylformamide afforded excellent yields of the desired 2-azolyl-4-phenoxypyrimidines of formula **1c**.

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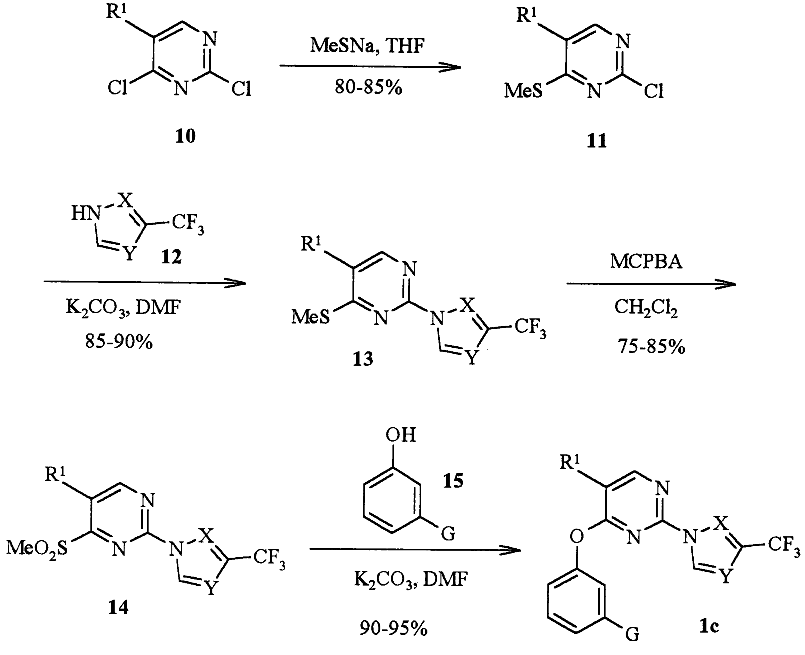
R1
N
Cl
N
Cl
10
MeSNa, THF
80-85%
R1
N
MeS
N
Cl
11
HN
X
CF3
Y
12
K2CO3, DMF
85-90%
R1
N
MeS
N
N
X
CF3
Y
13
MCPBA
CH2Cl2
75-85%
R1
N
MeO2S
N
N
X
CF3
Y
14
OH
15
G
K2CO3, DMF
90-95%
R1
N
O
N
N
X
CF3
Y
G
1c

R^1 = alkyl, MeO, halogen
G = CF_3, OCF_3, $OCHF_2$, SCF_3
X= N, CH; Y = N, CH, CCl, CCN

Figure 3. Regioselective Synthesis of Substituted 4-Phenoxy-2-azolylpyrimidines

Analogs were also made via a modification of this regioselective route by solid-phase synthesis. For example, Figure 4 shows the preparation of other phenoxy-substituted pyrazolylpyrimidines via a new thiobutyramide linker. Reaction of aminomethyl polystyrene with thiobutyrolactone gave resin-supported thiobutyramide **16** which on coupling with 2,4-dichloro-5-methyl-pyrimidine in the presence of Hunig's base in *N,N*-dimethylformamide provided **17**. The 2-chloro substituent on **17** was displaced with 3-trifluoromethylpyrazole in the presence of DBU in *N,N*-dimethylformamide, followed by oxidation of the methylthio group with *m*-CPBA, to give the polymer-supported intermediate of formula **18**. Displacing the sulfonyl group on **18** with 3-substituted phenols of formula **15** in the presence of DBU in dichloroethane released the final products of formula **1d** (with the G values shown in Figure 4) from the resin.

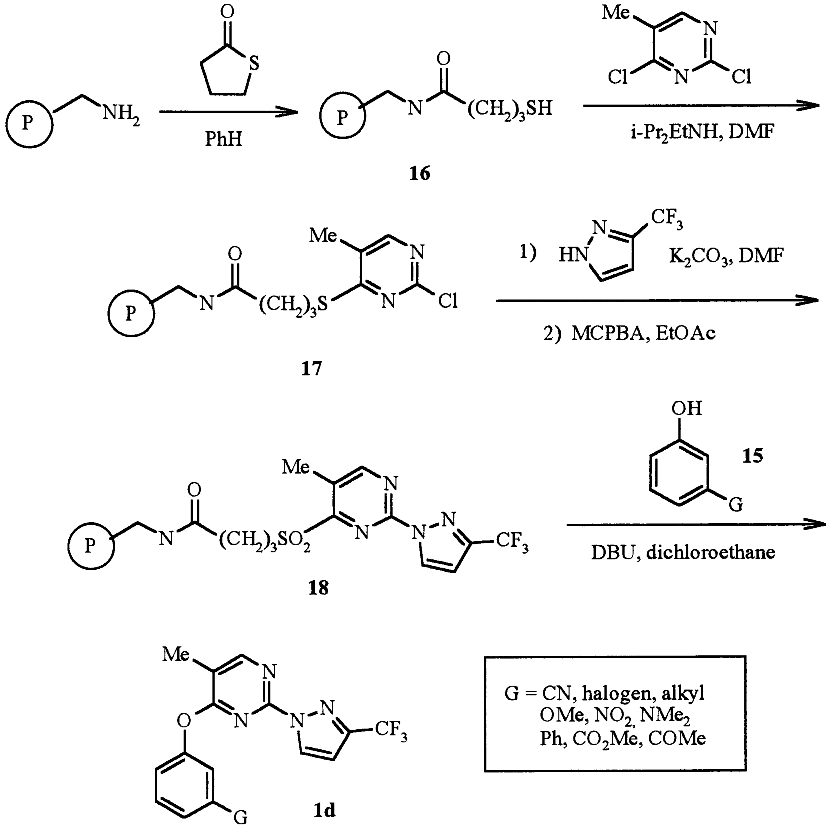
O
S
P
NH_2
PhH
O
N
$(CH_2)_3SH$
16
Me
N
Cl
N
Cl
$i\text{-}Pr_2EtNH$, DMF
O
Me
N
$(CH_2)_3S$
N
Cl
17
1)
N
CF_3
HN
K_2CO_3, DMF
2) MCPBA, EtOAc
O
Me
N
$(CH_2)_3SO_2$
N
N
N
CF_3
18
OH
15
G
DBU, dichloroethane
Me
N
O
N
N
N
CF_3
G
1d
G = CN, halogen, alkyl
OMe, NO_2, NMe_2
Ph, CO_2Me, COMe

Figure 4. Solid Phase Synthesis of Substituted 4-Phenoxy-2-pyrazolylpyrimidines

Finally, the synthesis of some substituted 4-heteroaryloxy-2-pyrazolylpyrimidines is shown in Figure 5. Reaction of 2-pyrazolyl-5-methyl-4-methylsulfonylpyrimidine **14a** with 2-hydroxy-6-trifluoromethylpyridine (*8*), 3-hydroxy-5-trifluoromethylthiophene (*9*) and commercially available 5-hydroxy-1-methyl-3-trifluoromethylpyrazole in the presence of potassium carbonate in *N,N*-dimethylformamide provided excellent yields of the 4-heteroaryloxy-2-pyrazolylpyrimidines **19**, **20** and **21**, respectively.

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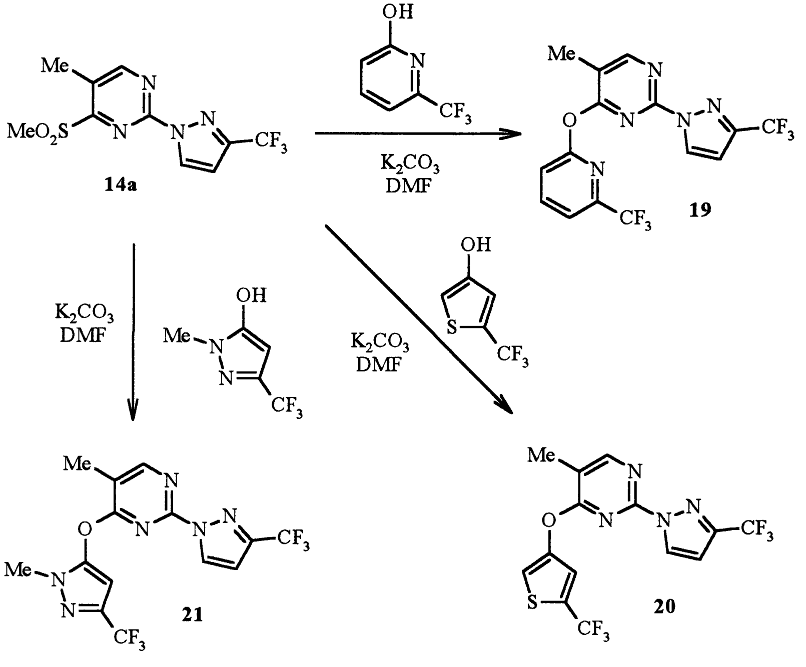


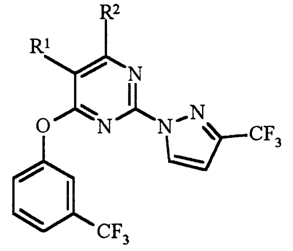
Figure 5. Synthesis of Substituted 4-Heteroaryloxy-2-pyrazolylpyrimidines

Biology & Structure-Activity Relationships

Compounds from this chemistry class were active preemergence and postemergence but tended to be more active when applied preemergence or early postemergence. They were active on both grass and broadleaf weeds and showed selectivity on crops including cereals, corn and soybeans. In Tables I and II, averaged preemergent herbicidal activity is summarized on the following weeds: morning glory (*Ipomoea hederacea*), velvetleaf (*Abutilon theophrasti*), crabgrass (*Digitaria sanguinalis*), giant foxtail (*Setaria faberii*), barnyardgrass (*Echinochloa crus-galli*) and wild oats (*Avena fatua*).

Table I shows preemergent data for 4-(3-trifluoromethylphenoxy)-2-(3-trifluoromethylpyrazolyl)-pyrimidines with substitution varied at the 4 and 5-positions on the central pyrimidine ring at rates of 400 and 125 g/ha. At 400 g/ha and where R^1 and R^2 are hydrogen and/or methyl, the highest level of activity was obtained when R^1 is methyl and R^2 is hydrogen. Moderate activity was observed where R^1 and R^2 are both hydrogen and significantly lower levels of activity were obtained for both analogs where R^1 is H or methyl and R^2 is methyl. At a lower rate of 125 g/ha and where R^2 is held constant as hydrogen, R^1 equal to ethyl or methyl gave the highest levels of activity with lower efficacy observed for larger or branched alkyl, methoxy, hydrogen or halogen.

Table I. Preemergent Herbicidal Activity of Substituted 4-(3-Trifluoromethylphenoxy)-2-(3-trifluoromethylpyrazolyl)pyrimidines



Average % Weed Control of Broadleaf and Grass Weeds[a]

R^1	R^2	400 g/ha	R^1	R^2	125 g/ha
			Et	H	>95
Me	H	>95	Me	H	95
H	H	85	*n*-Pr	H	90
Me	Me	70	OMe	H	80
H	Me	50	H	H	65
			i-Pr	H	50
			Cl	H	45

[a] Approximated values

Table II summarizes averaged preemergent activity and crop safety (on wheat, corn and soybeans) for substituted 2-azolyl-4-phenoxypyrimidines at 62 and 31 g/ha. Ethyl-substituted pyrazolylpyrimidines, where R^1 = Et, G is CF_3 or OCF_3, X = N and Y = CH, provided optimum levels of activity in greenhouse testing followed closely by their methyl-substituted pyrazolylpyrimidine counterparts (where R^1 is methyl). These compounds continued to provide broad-spectrum activity at 31 g/ha and showed good crop safety, although with some observed crop phytotoxicity. Triazolylpyrimidines

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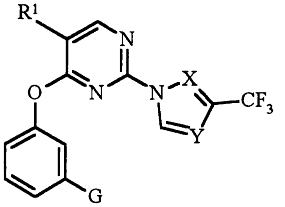
where R^1 is Et or Me, G is CF_3 or OCF_3, X is N and Y is N, were slightly less active than the pyrazolylpyrimidines and a further drop in activity was observed for imidazolylpyrimidines, where R^1 is Et or Me, G is CF_3 or OCF_3, X is CH and Y is N. No substantial improvement in crop safety was observed with either triazolylpyrimidines or imidazolylpyrimidines over pyrazolylpyrimidines.

Table II. Preemergent Herbicidal Activity of Substituted 2-Azolyl-4-phenoxypyrimidines



				Average % Weed Control[a]		*Average % Crop Injury*[b]	
R^1	G	X	Y	62 g/ha	31 g/ha	62 g/ha	31 g/ha
Et	CF_3	N	CH	95	90	<15	<10
Et	OCF_3	N	CH	95	90	<15	<10
Me	CF_3	N	CH	90	85	<10	<5
Me	OCF_3	N	CH	90	85	<10	<5
Et	CF_3	N	N	90	85	<10	<10
Et	OCF_3	N	N	85	80	<10	<10
Me	CF_3	N	N	85	80	<10	<10
Me	OCF_3	N	N	85	75	<10	<5
Et	CF_3	CH	N	80	75	<10	<5
Et	OCF_3	CH	N	80	70	<5	<5
Me	CF_3	CH	N	75	70	<10	<5
Me	OCF_3	CH	N	70	65	<5	<5
Me	CF_3	N	CCN	70	60	<5	<5
Me	CF_3	N	CCl	65	55	<5	0
Me	$OCHF_2$	N	CH	60	40	0	0
Me	SCF_3	N	CH	55	30	0	0

[a] Approximated activity against broadleaf and grass weeds

[b] Approximated injury to wheat, corn & soybeans

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The lowest levels of activity shown in Table II were exhibited by pyrazolylpyrimidines where R^1 is Me, G is CF_3, X is N and Y is CCN or CCl and pyrazolylpyrimidines where R^1 is Me, G is $OCHF_2$ or SCF_3, X is N and Y is CH.

Although this class of chemistry showed selectivity on cereals, corn and soybeans, these compounds were of most interest for preemergent and early post-emergent weed control in cereals. On some weeds, high activity was obtained at very low rates of application.

Mode-of-Action

The mode-of-action for this class of chemistry was shown to be inhibition of phytoene desaturase in the carotenoid biosynthesis pathway. To a cell-based assay comprising *E. coli* cells expressed with the *Arabidopsis* gene for phytoene desaturase (*10*), application of these compounds gave rise to a buildup of the phytoene substrate at the expense of *zeta*-carotene formation. This showed that test compounds interfered with the enzyme phytoene desaturase and thereby blocked carotenoid biosynthesis. Since carotenoids protect chlorophyll, and ultimately the chloroplast, from photooxidative degradation by sunlight, the herbicidal effect of these compounds results from loss of carotenoids, making the plant susceptible to damage by sunlight. Loss of carotenoids and chlorophyll pigments results in the characteristic bleached appearance (albinism) on treated plants.

Cereal Field Testing

Several pyrazolylpyrimidines of formula **1** (where R^1 is Et or Me, R^2 is H, G is CF_3 or OCF_3, X is N and Y is CH) were evaluated as wheat herbicides for preemergent and early postemergent weed control. Some analogs showed excellent broad-spectrum premergent activity against grass and broadleaf weeds at rates between 50 and 100 g/ha. Good wheat safety was also observed but generally with some early transient crop phytotoxicity, especially at the higher application rates required for grass control. Although analogs where R^1 is ethyl were generally more active than analogs where R_1 is methyl in greenhouse testiing, **1a** was actually found to have optimum field activity and continued to provide excellent preemergent and early postemergent control of small-seeded broadleaf weeds at rates at low as 5-10 g/ha.

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Conclusion

Substituted *N*-azolyl phenoxyprimidines of formula **1** represent a new family of highly active herbicides that inhibit phytoene desaturase in the carotenoid biosynthesis pathway. Compounds from this class showed broad-spectrum preemergent and early postemergent activity against broadleaf and grass weeds with selectivity on cereals and other crops. In cereal field trials, pyrazolylpyrimidines provided broad-spectrum weed control and good wheat safety. Compound **1a** gave optimum field activity with excellent broadleaf weed control at rates as low as 5-10 g/ha. However, commercial development of **1a** was not pursued due to a narrow margin of crop safety at high rates of application and concerns regarding soil persistence.

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Chapter 9

2-Azolyl-4-Benzylpyrimidine Herbicides: Novel Inhibitors of Carotenoid Biosynthesis Part II

Thomas M. Stevenson, Thomas P. Selby, Gerard M. Koether, Joseph E. Drumm, Xian J. Meng, M. P. Moon, Reed A. Coats, Tho V. Thieu, Albert E. Casalnuovo, and Rafael Shapiro

Stine-Haskell Research Center, DuPont Crop Protection,
Newark, DE 19714

2-Azolyl-4-benzylpyrimidines have high activity as herbicides. These compounds can be made by palladium-catalyzed cross coupling reactions of 2,4-dichloropyrimidines with benzylic zinc reagents followed by nucleophilic substitution with azoles. Optimally substituted compounds have excellent activity on broad-leaved weeds and grasses. Highest levels of activity are observed in pre-emergence application, but good activity is also seen in post-emergence tests. Good tolerance is shown by a variety of crops, notably cereals. Cereals field-testing proved these compounds to have commercial levels of pre-emergence activity against all major European broadleaf weeds at 5-15 g/ha. with excellent crop tolerance. At 50-100 g/ha. good control of all important grasses was also displayed.

Introduction

The discovery of excellent herbicidal activity for 2-azolyl-4-phenoxypyrimidines such as **1** (*1*) prompted us to explore structural modifications of these compounds. Our goal in this work was to replace the phenoxy group with more readily degraded isosteric substituents such as benzyl or benzoyl as in compouunds **2** and **3** (Figure 1). We hoped that this would lead

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to compounds which retained the excellent biological activity of the phenoxypyrimidines, but had improved soil metabolism.

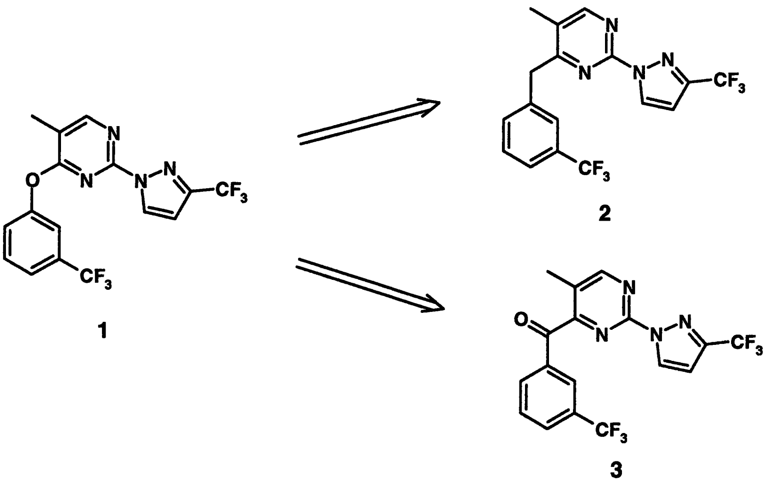
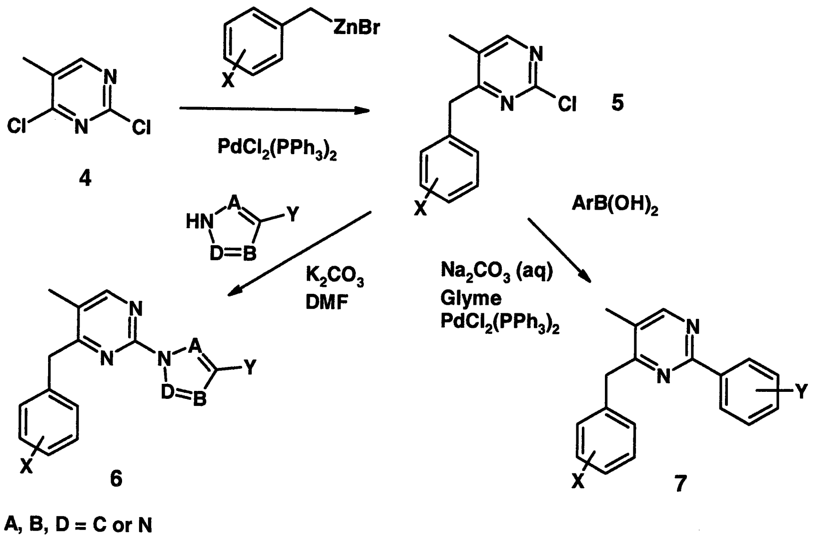


Figure 1. Benzyl and Benzoyl Pyrimidines

Chemistry

The synthesis of benzyl substituents in heterocycles has traditionally been done by including them in the starting materials of a multistep route or by introducing them via nucleophilic displacement with phenylacetic acid derivatives followed by decarboxylation. We thought that a more straightforward route would be to introduce a benzyl group by palladium-catalyzed cross-coupling of benzyl zincs with chloropyrimidines. This would allow us to use the same pyrimidine starting materials that were available from the 2-azolyl-4-phenoxypyrimidine project. Benzyl zinc reagents can be made in excellent yields by using zinc activated by Knochel's method (*2*) with benzyl chlorides or bromides. We found that 3-trifluoromethylbenzylzinc bromide was readily made by adding the corresponding bromide to 2 eq. of activated zinc in tetrahydrofuran. Adding the zinc reagent to 2,4-dichloro-5-methylpyrimidine **4** in the presence of a palladium catalyst gave the benzylpyrimidine **5** (X = 3-CF_3) in good yield. Displacement of the remaining chlorine by 4-trifluoromethylpyrazole in dimethylformamide with potassium carbonate as the base gave the desired pyrimidine **6** (X = 3-CF_3, Y = CF_3, A = N, D and B = CH). In contrast to the 4-phenoxypyrimidines, 2-arylpyrimidines **7** were novel in this series so we also carried out a Suzuki coupling (*3*) of **5** with 4-trifluoromethylphenylboronic acid. This palladium catalyzed cross coupling also proceeded readily to give the 2-aryl product **7** (X = 3-CF_3, Y = 4-CF_3) . The initial products from the sequence showed excellent activity (*4*) as herbicides and an analoging program was begun as shown in Scheme 1. Extension of the benzyl coupling reaction to other benzyl bromides and other pyrimidines was possible. A variety of other pyrazoles, triazoles and imidazoles as well as boronic acids were used in optimization of the area.



Scheme 1. Analog Synthesis Method

The benzylic position of **6** provided a handle for the introduction of a variety of substituents. Alkylation of the very acidic benzylic-position was possible using sodium hydride as base as exemplified in Scheme 2 with methyl iodide to produce **8**. Free radical chlorination with sulfuryl chloride gave the benzylic chloride **9**. This interesting intermediate could be further functionalized by nucleophiles such as sodium methoxide to give pyrimidine **10**.

Our next set of targets were 2-azolyl-4-benzoylpyrimidines **3**. Recent work by Miyashita (*5*) suggested a direct route was also possible for the 4-benzoylpyrimidines. His group has found that with certain catalysts benzaldehydes can acylate chloroheterocycles. Reaction of 1,3-dimethylimidazolium iodide, sodium hydride, pyrimidine **4** and 3-trifluoromethylbenzaldehyde gave a good yield of the desired benzoylpyrimidine **11**. Displacement of the remaining chlorine from **11** with 4-trifluoromethylpyrazole was easily accomplished to give pyrimidine **3** which exhibited promising activity. Suzuki coupling of **11** with 4-trifluoromethyl-phenylboronic acid gave the 2-arylpyrimidine **12**. The route shown in Scheme 3 could be extended to other aldehydes, pyrimidines, azoles and boronic acids to complete an analoging program.

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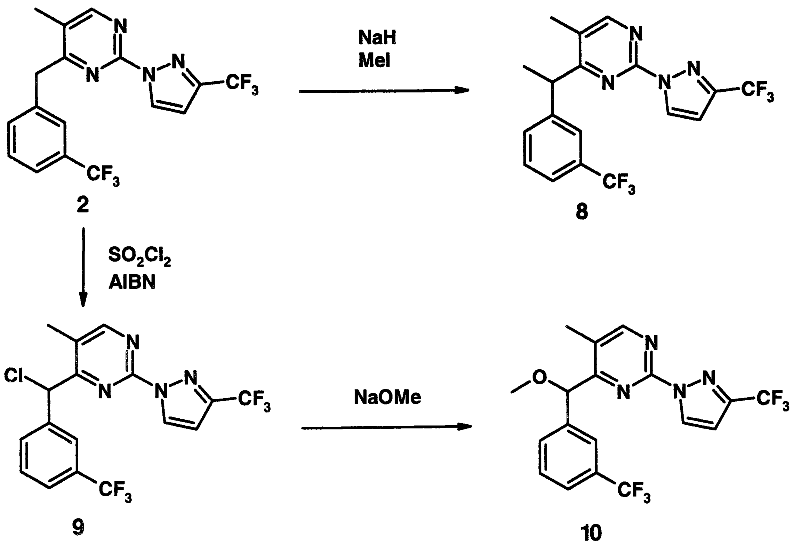
N
N
N
N
CF3
CF3
2
NaH
MeI
8
SO2Cl2
AIBN
Cl
9
NaOMe
O
10

Scheme 2. Modification of the Benzylic Position

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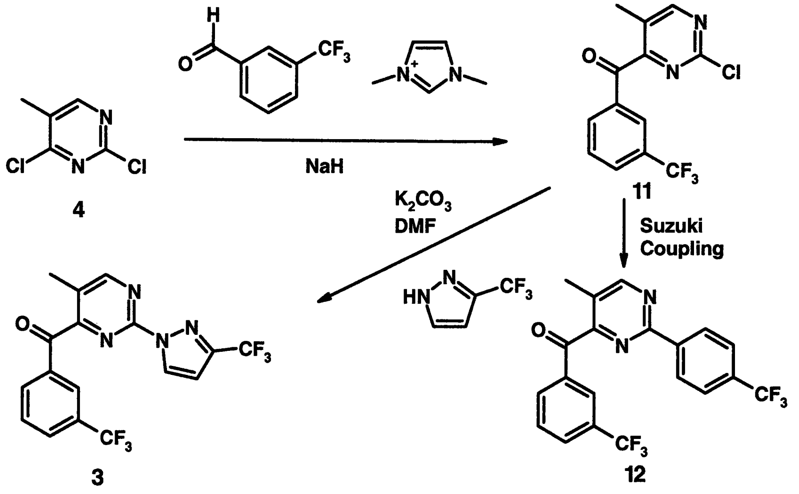

Scheme 3. Analog Program for 4-Benzoylpyrimidines

The benzylic substituent provided another opportunity for expanding the scope of the pyrimidine herbicides. The ability of azoles in compounds **1** to act as isosteres of *para*-substituted phenyl groups in compounds like **13** provided the impetus to make the pyrimidines we have described in this paper. We wondered if azoles could also replace the benzylic substituent in compounds such as **14**. In this instance they would have to act as isosteres of *meta*-substituted phenyls. Conceptually this is shown in Figure 2.

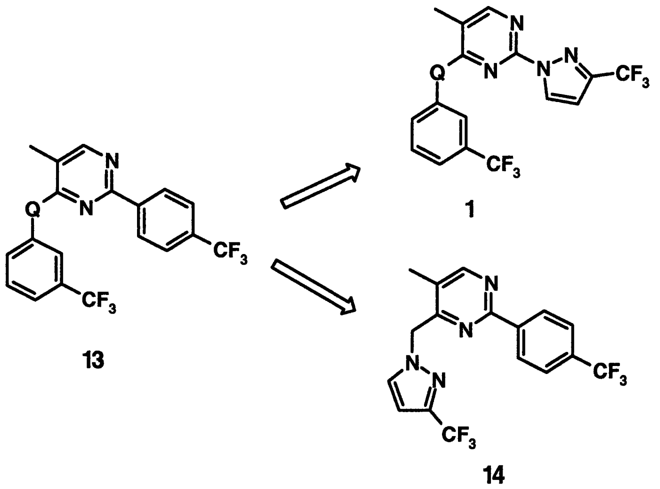

Figure 2. Trifluoromethyl Azoles as Aryl Replacements

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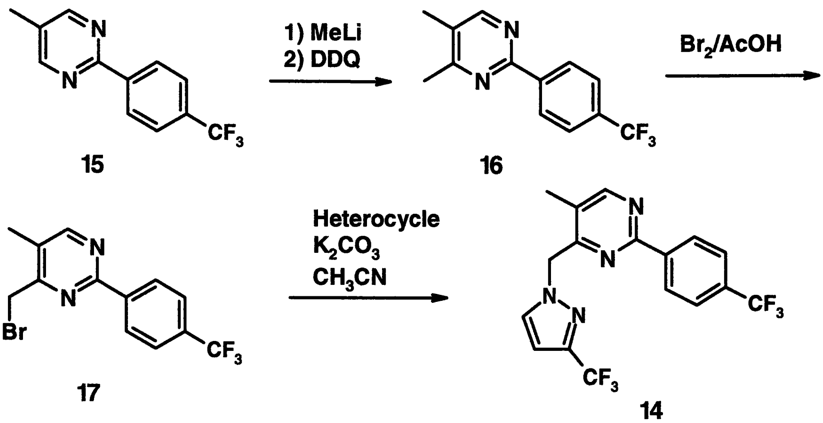
We hoped that we could make the target azolylmethylpyrimidines by the displacement of 4-bromomethyl pyrimidines. Several ways to make haloalkylpyrimidines exist, but we chose Strekowski's pyrimidine functionalization (*6*) as the most expeditious synthetic solution. Beginning with pyrimidine **15** we introduced a methyl at the 4-position by the addition of methyl lithium and *in-situ* DDQ oxidation of the resulting dihydropyrimidine gave pyrimidine **16**. Selective bromination of the 4-methyl group was achieved with bromine in acetic acid to give **17** (N-Bromosuccinimide in carbon tetrachloride gave bromination on the 5-methyl). This unstable benzyl bromide **17** was used to alkylate a variety of different substituted azoles on nitrogen to give pyrimidine **14** and analogs (Scheme 4). Herbicidal activity for **14** confirmed the ability of azoles as isosteres of both *meta-* and *para*-substituted benzenes.



Scheme 4. Synthesis of an Azolylmethylpyrimidine

With this result in hand we set out to make a pyrimidine in which azoles could serve to mimic both substitution patterns while in the same molecule. To synthesize these targets we used a slightly different reaction sequence (Scheme 5). Beginning with 2,4-dichloro-5-methylpyrimidine **4** we selectively introduced a methyl group into the 4-position by a palladium-catalyzed addition of trimethylaluminum (*7*) to give **18**. Selective bromination of **18** with bromine in acetic acid gave **19**. The benzyl halide in **19** reacted at room temperature with azoles to give the 4-azolylmethylpyrimidine **20** with a reactive 2-chloro substitutent. Introduction of the second azole group was done at 60 – 80 ° C. to give **21**. By changing the order in which the azoles were introduced a variety of different bis-azolylpyrimidines were synthesized and evaluated.

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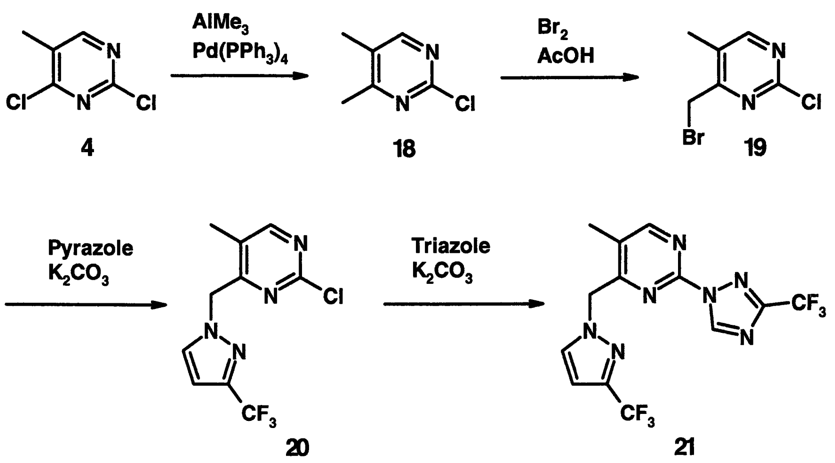

Scheme 5: Pyrimidines with Two Azoles

Biology and Structure-Activity Relationships

The compounds discussed above had excellent levels of herbicidal activity. Both pre-emergence and post-emergence activity was exhibited by a variety of compounds on broadleaf and grass weeds. Generally, the pre-emergence activity was superior. As is typical of inhbitors of carotenoid biosynthesis (*1*), the herbicidal effect of these pyrimidines was expressed as albinism. The benzylpyrimidines showed very high activity and had comparable levels of activity and even better crop safety than the phenoxypyrimidines. The benzoylpyrimidines while very active at rates of 125 g/ha. and above, were substantially less active than compounds with O and CH_2 linkers at lower rates. In Table I averaged preemergent herbicidal activity is summarized on the following weeds: morning glory (*Ipomoea hederacea*), velvetleaf (*Abutilon theophrasti*), crabgrass (*Digitaria sanguinalis*), giant foxtail (*Setaria faberii*), barnyardgrass (*Echinochloa crus-galli*) and wild oats (*Avena fatua*). Summarized crop injury is averaged from wheat, corn and soybeans.

Other aspects of structure-activity relationships are outlined in Figure 3. For the R-substituent at position 5 small alkyl groups proved to be optimal. At the benzylic position all substitution reduced activity substantially. On the benzyl aryl ring only compounds with *meta*-substitution had high activity. The best substituents at this position were haloalkyl and haloalkoxy. A comparison of R^1 substituents at the pyrimidine 2-position showed that haloalkylazoles had higher activity than their phenyl counterparts. Of the various azoles investigated pyrazoles were slightly better than triazoles and imidazoles. For 2-phenylpyrimidines *para*-substitution was preferred and trifluoromethyl was the best substituent.

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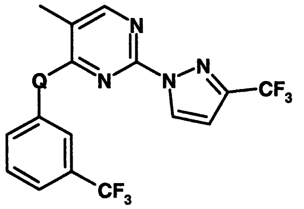
Table I. Pre-emergence Herbicidal Activity for Varied Linkers


N
Q
N
N
N
CF3
CF3

	Average % Weed Control[a]		*Average % Crop Injury*[b]	
Q	62 g/ha	31 g/ha	62 g/ha	31 g/ha
O	90	85	< 10	< 5
CH_2	90	80	< 5	< 5
CO	70	45	< 5	< 5

[a] Approximated activity against broadleaf and grass weeds

[b] Approximated injury to wheat, corn and soybeans

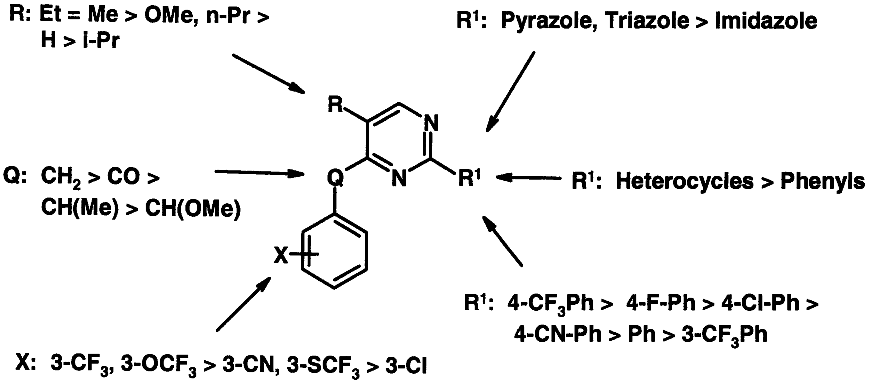

R: Et = Me > OMe, n-Pr > H > i-Pr
R¹: Pyrazole, Triazole > Imidazole
Q: CH2 > CO > CH(Me) > CH(OMe)
R¹: Heterocycles > Phenyls
R¹: 4-CF3Ph > 4-F-Ph > 4-Cl-Ph > 4-CN-Ph > Ph > 3-CF3Ph
X: 3-CF3, 3-OCF3 > 3-CN, 3-SCF3 > 3-Cl
R
N
N
Q
R¹
X

Figure 3: Structure Activity trends for Herbicidal Pyrimidines

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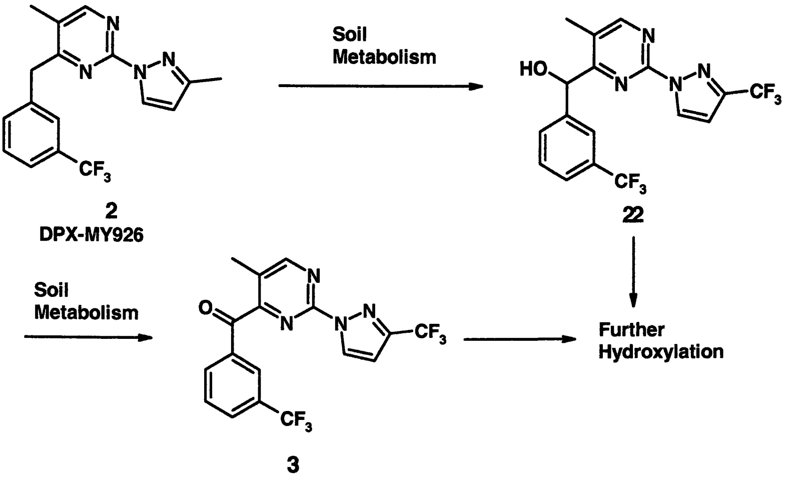
Azolylmethylpyrimidine **14** had good activity at 125 g/ha. Bis-azolylmethylpyrimidines like **20** had better activity and **20** itself was unbroken on several weeds at 31 g/ha. Some interesting differences were seen between the optimal azoles at the benzylic position and at the 2-position of the pyrimidine. At the 2-position in which the azoles are isosteres of *para*-substituted phenyls; pyrazoles, imidazoles and triazoles showed fairly similar levels of activity. However, at the benzylic position where they need to be isosteric to a *meta*-substituted phenyl, pyrazoles have considerably more activity than the other azoles. On the pyrazole the 3-position was the optimal position for substitution. While highest activity was seen for 3-trifluoromethylpyrazoles, additional substituents such as cyano or chloro at the 4-position reduced activity. Interestingly, while addition of a 5-methyl on the pyrazole of **14** decreased overall activity, phytotoxicity on foxtail and other related grasses as well as pigweed was retained at low rates.

Soil Metabolism

One advantage of replacing the 4-phenoxy substituent with a benzylic group was its improved potential for metabolic oxidation. We hoped that it would undergo degradation by both environmental conditions and by biological systems. One compound DPX-MY926 **2** was studied closely and found to be degraded by soil microbes to give a variety of oxidation products including benzoylpyrimidine **3** (Scheme 6). Both hydroxylation at the benzylic position and at the 5-methyl group were observed.



Scheme 6. Soil Degradation Routes for a Pyrimidine Herbicide

Cereal Field Testing

The high levels of activity seen for the compounds in the greenhouse and potential for environmental degradation led us to evaluate DPX-MY926 (**2**) in a number of field trials in cereals. A variety of different treatment regimens were investigated. When MY926 was applied to winter wheat soon after germination (early post-emergence application) and the field evaluated in the spring an amazing level of control of all broadleaf weeds was observed even at rates as low as 5 g/ha. In traditional pre-emergence application MY926 controlled these key weed species at 10-15 g/ha. However, the key grasses were not controlled at these rates. Nonetheless, raising the application rates to 50-80 g/ha. gave total weed control of grasses and broadleaf weeds. At these higher rates the excellent safety margin seen at lower rates was lessened.

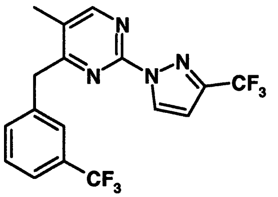


Figure 7. DPX-MY926 Cereal Herbicide

Conclusions

In conclusion we have shown that benzylpyrimidine herbicides have excellent potential as crop protection agents. They have shown extremely high levels of activity and have good safety to major crops. In addition they have shown the potential for environmental degradation.

Acknowledgments

We would like to thank James V. Hay, Charles R. Harrison and Russell F. Bellina for their support of this project. The field studies for this area were conducted by Jean-Pierre Claude. Soil metabolism studies were carried out by Chris Petersen.

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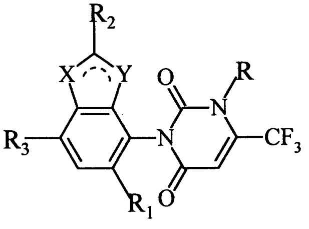
Chapter 10

Synthesis and Structure–Activity of Novel 3-(4,6-substituted benzoheterocyclyl)uracil Herbicides

George Theodoridis, James T. Bahr, Scott Crawford, Benjamin Dugan, Frederick W. Hotzman, Lester L. Maravetz, Saroj Sehgel, and Dominic P. Suarez

Agriculture Products Group, FMC Corporation, P.O. Box 8, Princeton, NJ 08543

3-(4,6-Substituted benzoheterocycl-7-yl)-1-substituted-6-trifluoromethyl uracils **1** represent a novel class of highly active pre- and postemergent herbicides, which act by inhibition of the plant enzyme protoporphyrinogen oxidase (Protox). The synthesis, biological activity, and structure-activity of these new herbicides will be discussed.



1

Research directed towards the discovery of molecules that inhibit the plant enzyme protoporphyrinogen oxidase (Protox) has resulted in a wide variety of

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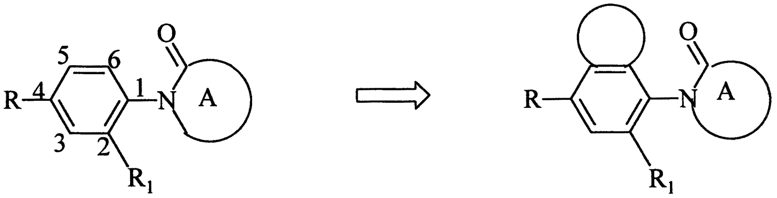
highly potent pre- and postemergent herbicides (*1*). A striking feature of Protox herbicides is the large number of different families of chemistries, each with its unique set of structure-activity rules, that can act by this mode of action (*2,3,4*).

Here, we wish to report on a new chemistry class of Protox herbicides, 3-(4,6-substituted benzoheterocyclyl)uracils, structure **2**, where positions 5 and 6 of the aromatic ring are tied together to form a new ring, Figure 1. The resulting benzoheteroaryl compounds are highly potent pre- and postemergent herbicides.



2

Figure 1. Fused Benzoheterocyclic Ring Systems.

In general, the chemical structure of Protox herbicides consists of a substituted aromatic ring attached to a heterocyclic ring (*1*). A wide range of substituted heterocycles, attached to aromatic rings having specific substitution patterns, are known to provide good biological activity. Unlike previous Protox herbicide chemistries, the nature of the heterocyclic ring A, shown in Figure 1, plays a crucial role in the biological activity of compounds with structure **2**. We will be discussing the structure-activity requirements for this new class of herbicides.

Biological Testing

The compounds described were tested pre- and postemergence on various weeds and crops in the greenhouse. The seeds of the plant test species were planted in furrows in steam-sterilized sandy loam soil contained in disposable fiber flats. A topping soil of equal portions of sand and sandy loam soil was placed uniformly on top of each flat to a depth of approximately 0.5 cm.

The flats were placed in a greenhouse and watered for 8-10 days, then the foliage of the emerged test plants was sprayed with a solution of the test compound in acetone-water containing up to 5 ml liter $^{-1}$ sorbitan monolaurate emulsifier/solubilizer. The concentration of the test compound in solution was varied to give a range of application rates. Phytotoxicity data were taken as percentage control, determined by a method similar to the 0-100 rating system described previously *(5)*, with 0% control of crops or weeds showing no effect relative to controls, and 100% control indicating complete crop or weed destruction. Biological data in Tables 1-4 are presented as the preemergence and postemergence application rates required to give 85% control as compared with untreated plants.

Synthesis of benzoheterocycyluracil Herbicides

Uracil Ring Synthesis

The uracil portion of the molecule was prepared in good yields from the corresponding aryl isocynate **3**, obtained from the reaction of the aryl amine **2** and phosgene, or a phosgene substitute, and ethyl trifluoromethylaminocrotonate in the presence of a base. Addition of an alkyl halide gave the corresponding N-alkyl product **4**, Figure 2.

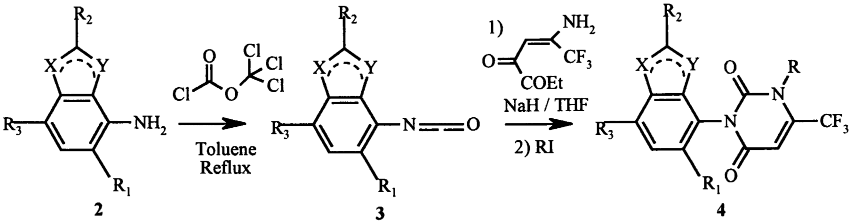


Figure 2. General Synthesis of the Uracil Ring.

Fused Ring Synthesis

A complete review of the synthesis of each of the many hetererocycles prepared for this project is beyond the scope of this work. We will only highlight the synthesis of several of the most significant benzoheterocycles.

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7-Amino-2,3-Dihydrobenzofuran Derivatives

The various 7-amino-2,3-dihydrobenzofuran intermediates were prepared in several steps from 5-chloro-2-nitrophenol. Claisen rearrangement of 4-chloro-2-(2-methyl-2-propen-1-yloxy)nitrobenzene **5**, followed by ring formation in the presence of catalytic amounts of $MgCl_2$ gave 4-chloro-7-nitro-2,3-dihydrobenzofuran **6**. Oxidation of the 4-methylene group of compound **6** with potassium persulfate in the presence of copper sulfate in acetonitrile/water, gave compound 7. Reduction of the nitro group with iron/acetic acid gave the desired 7-amino-4-chloro-2,3-dihydrobenzofuran **8** (*6*), Figure 3.

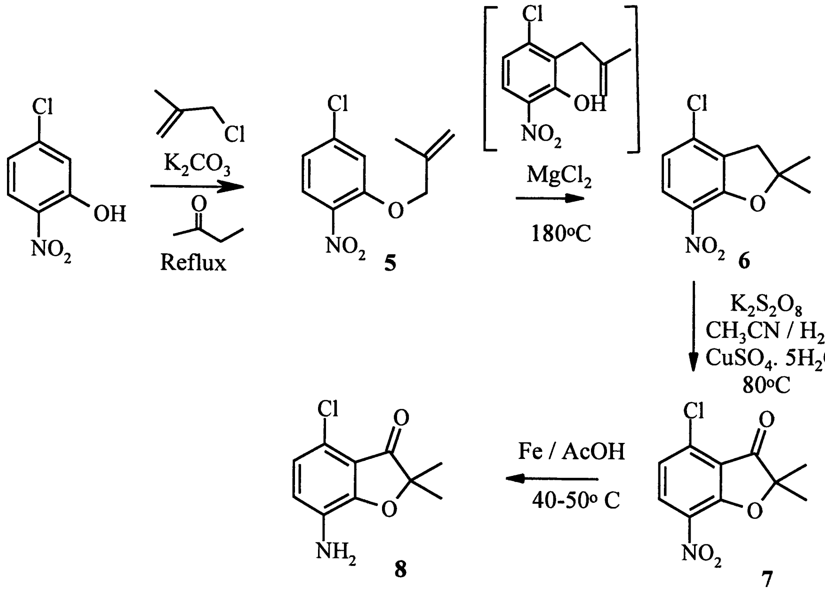

Figure 3. Synthesis of 7-amino-4-choro-2,3-dihydrobenzofuran.

7-Amino Benzodioxolane Derivatives

The desired 7-amino benzodioxolane compounds were prepared from the reaction of 5-fluoro-2,2-dimethyl-1,3-benzodioxole, obtained from the reaction of 1-fluoro-3,4-dihydroxybenzene **10** and acetone in the presence of P_2O_5, and n-butyl lithium followed by addition of carbon dioxide to give the corresponding carboxylic acid derivative **12**. Curtius rearrangement of

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compound **12** with diphenylphosphoryl azide resulted in 7-amino-6-fluoro-2,2-dimethyl-1,3-benzodioxole **13**. Chlorination of compound **13** with N-chlorosuccinimide in DMF gave the corresponding 7-amino-4-chloro-6-fluoro-2,2-dimethyl-1,3-benzodioxole **14** (*7*), Figure 4.

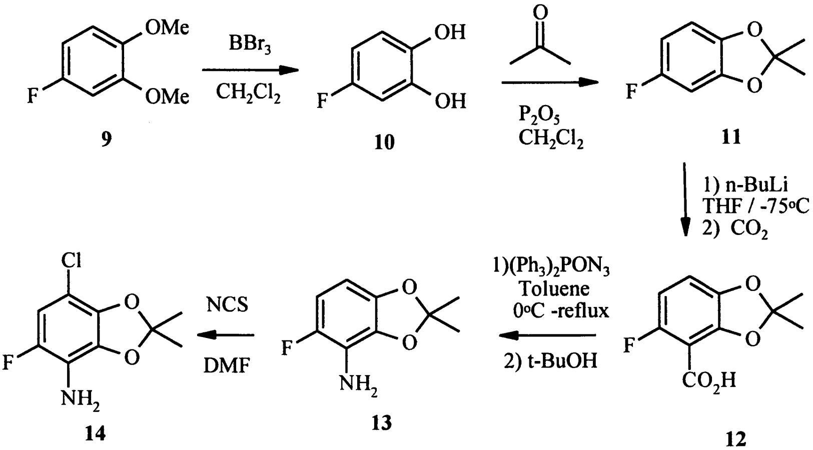

Figure 4. Synthesis of 7-Amino-4-chloro-6-fluoro-1,3-benzodioxolane.

Amino Benzoisoxazole Derivatives

Treatment of 2-chloro-3-nitrobenzoic acid with thionyl chloride in toluene gave the corresponding acid chloride **15**. Reaction of 2-chloro-3-nitrobenzoyl chloride with N-substituted hydroxylamine gave compound **16**, which was cyclized to 7-nitrobenzoisoxazole **17** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile. Reduction of **17** with iron in acetic acid at 50°C, followed by chlorination with N-chlorosuccinimide gave the desired 7-amino-4-chloro-isoxazol-3-one **19** (*8*), Figure 5.

Structure-Activity Relationships

Effect of Heterocyclic Ring on Biological Activity

Unlike other Protox chemistries, in the benzoheterocyclic chemistry discussed in this chapter, only certain heterocyclic rings resulted in highly active molecules. As shown below, replacement of the triazolinone ring in compound **20** with a uracil ring, compound **21**, resulted in a dramatic increase in biological activity,

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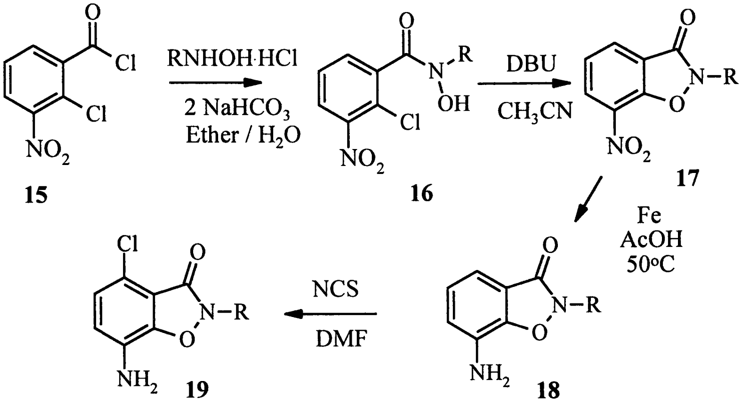
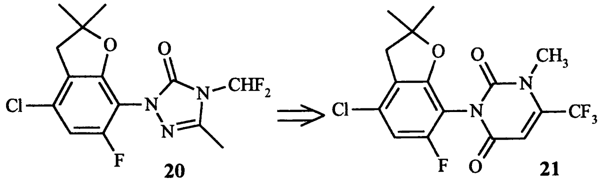

RNHOH·HCl
2 NaHCO$_3$
Ether / H$_2$O
DBU
CH$_3$CN
Fe
AcOH
50°C
NCS
DMF
15
16
17
18
19

Figure 5. Synthesis of 7-Amino-4-chloro-benzoisoxazole.

Figure 6. The triazolinone ring has previously resulted in highly active molecules, including several commercial herbicides (*9*).



Preemergence Biological Activity ED$_{85}$ g/ha		
Morningglory	395	22
Johnson grass	300	10

Figure 6. Comparison of Triazolinone and Uracil Rings.

Effect of the Fused Benzoheterocyclic Ring System on Biological Activity

Though a large number of fused benzoheterocyclic rings were investigated, we will be presenting the results of only six different heterocycles. All these compounds have a uracil ring attached to the benzoheterocyclic ring. As shown in Table 1, although both five and six membered fused rings were biologically active, compounds having a five membered ring, such as 2,3 dihydrofuran-4-one **22**, isoxazol-4-one **23**, and dioxolane **24**, provided the highest biological activity. In general broadleaf weed control was greater than grass control when compounds **22-27** were applied preemergence.

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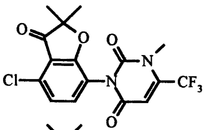
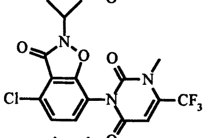
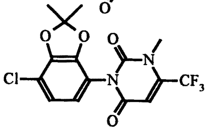
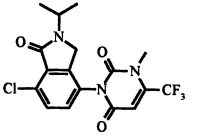
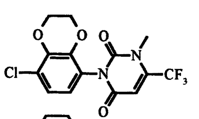
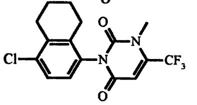
Table 1. Effect of Fused Benzoheterocyclic rings on Preemergence Biological Activity

Compound	*Preemergence Biological Activity ED_{85} g/ha*		
		Morningglory	Velvetleaf
22		6	2
23		8	2
24		20	4
25		58	14
26		100	19
27		643	84

Effect of the Substituents in Position 4 of the Fused Benzoheterocyclic Ring on Biological Activity

Several chemical groups were introduced at position 4 of the 2,3-dihydrobenzofuran ring. In general, electron withdrawing lipophilic groups such as compounds **22** (R= Cl) and **28** (R= Br), provided the best activity (Table 2). Electron donating groups such as methoxy, compound **32**, and dimethylamine, compound **33**, resulted in less active molecules.

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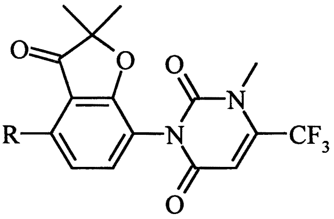
Table 2. Effect of Substituents at Position 4 of the Benzofuran ring on Preemergence Biological Activity

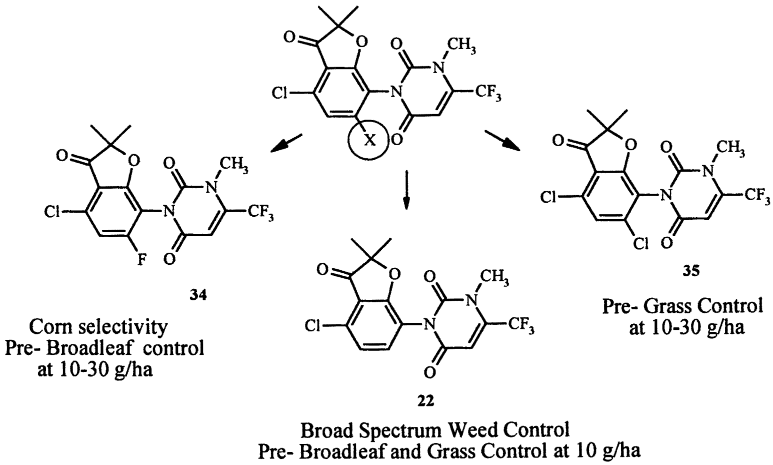


Preemergence Biological Activity		*ED85 grams/ha*	
Compound	R	Velvetleaf	Morningglory
22	Cl	2	6
28	Br	6	16
29	H	10	46
30	CH_3	26	26
31	F	24	57
32	OCH_3	74	91
33	$N(CH_3)_2$	233	>1000

Effect of Substituents at Position 6 of the Fused Benzoheterocyclic Ring on Biological Activity

Substituents at position 6 of the fused benzoheterocyclic ring had a dramatic effect on the weed spectrum and crop selectivity of these molecules when applied preemergence. This is clearly exemplified by the three 2,3-dihydrobenzofuran examples shown in Figure 7. Introduction of a fluorine at position six of the aromatic ring resulted in compound **34** which has excellent corn selectivity and control of broadleaf weeds at 10-30 grams/hectare. Next, replacing the 6-fluoro group with a chlorine group resulted in a molecule, compound **35**, which has good grass control at 10-30 grams/hectare.

Finally, compound **22**, with a hydrogen substituent at the 6-position resulted in broad spectrum control of both broadleaf and grass weeds at 10 grams/hectare. Preemergence application of compounds **22** and **35** resulted in corn injury at application rates that provided weed control. The weeds discussed in Figure 7 are velvetleaf, wildmustard and pigweed for the broadleaf weeds, and barnyardgrass, green foxtail, and johnson grass for the grass weeds.



34

Corn selectivity
Pre- Broadleaf control
at 10-30 g/ha

35

Pre- Grass Control
at 10-30 g/ha

22

Broad Spectrum Weed Control
Pre- Broadleaf and Grass Control at 10 g/ha

Figure 7. *Effect of Substituents at Position 6 of the 2,3-Dihydrobenzofuran ring on Biological Activity.*

It is important to point out that structure-activity relationships for position 6 of the benzoheterocycle are highly dependant on the nature of the heterocycle attached to the aromatic ring as shown below. Replacement of the carbonyl in

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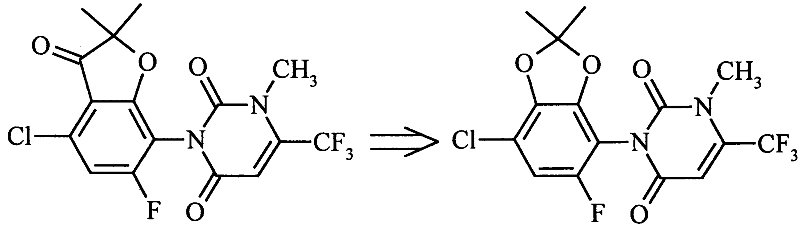
compound **34** with oxygen, to give compound **36**, resulted in loss of corn selectivity but increased weed spectrum and biological activity, Table 3.

Table 3. Effect of Benzohetero Ring on Preemergence Biological Activity



34 **36**

Greenhouse Preemergence Biological Activity (% control)				
Applied Rate (g / ha)	30	10	30	10
Corn	5	0	90	80
Pigweed	100	100	100	100
Wild Mustard	100	100	100	100
Velvetleaf	100	100	100	100
Green foxtail	95	25	100	100
Johnson grass	30	5	100	100

Effect of Substituents at Position 1 of the Uracil Ring on Biological Activity

A variety of substituents at position 1 of the uracil ring were investigated with a number of different benzoheterocyclic rings. The structure-activity relationship developed for the 3-benzodioxolane-1-substituted uracil ring shown in Table 4 applied to the other rings investigated. In general, it was found that small R groups resulted in the most active compounds. It is interesting to notice that both a lipophilic (R= CH_3, compound **36**) and a hydrophilic group (R= NH_2, compound **37**) had comparable biological activity, Table 4.

Finally, opening of the benzoheterocyclic ring resulted in significant loss of biological activity as shown in Figure 9. Compound **42**, were the two adjacent oxygens of the dioxolane ring are no longer tied together, is more than 10 times less active than its closed ring analog **36**, Figure 8.

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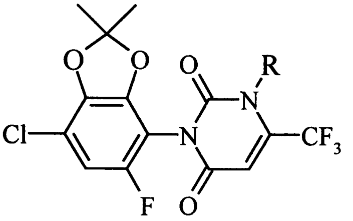
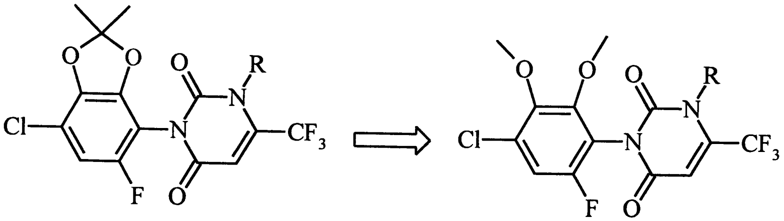
Table 4. Effect of Substituents at Position 1 of the Uracil Ring on Biological Activity



Preemergence Biological Activity ED_{85} grams/ha				
Compound	R	Velvetleaf	Morningglory	Green foxtail
36	CH_3	3	3	3
37	NH_2	3	3	3
38	CH_2CH_3	8	17	3
39	CH_2OCH_3	18	52	44
40	$CH_2C_6H_5$	958	>1000	307
41	$CH_2CH_2CH_3$	>1000	>10000	>1000



36 **42**

Pre-emergence Biological Activity ED_{85} g/ha		
Velvetleaf	3	32
Green foxtail	4	143

Figure 8. *Comparison of Biological Activity of Ring Close vs. Ring Open Heterocycles.*

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Summary

The 3-(4,6-Substituted benzoheterocyclyl)uracils **1** described in this chapter are highly active pre- and postemergence herbicides, with a broad spectrum of weed control. This highly versatile class of chemistry offers the potential for a variety of uses, such as preemergence control of broadleaf weeds and corn tolerance, compound **34**, or broad spectrum weed control at very low rates, compound **36**. The mechanism of action involves the inhibition of the plant enzyme protoporphyrinogen oxidase, which results in the buildup of high levels of protoporphyrin IX, a photodynamic toxicant.

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Publication Date: July 29, 2001 | doi: 10.1021/bk-2002-0800.ch010

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Chapter 11

Synthesis and Biological Activity of Indazole Insecticides

George P. Lahm, Charles R. Harrison, John P. Daub, Rafael Shapiro, Jeffrey K. Long, Donald E. Allen, Wendy A. March, Sandra M. Griswold, Robert W. March, and Bonita M. Reeves

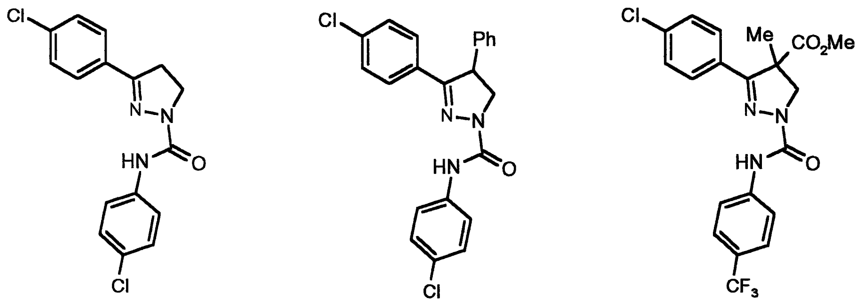
Stine-Haskell Research Center, DuPont Agricultural Products, Building 300, Newark, DE 19714

The discovery and development of the new commercial insecticide indoxacarb involved initial studies toward the synthesis and evaluation of a series of indazole insecticides. The target indazoles were selected based on pyrazoline insecticide models. The synthesis and insecticidal activity of these compounds is described.

The continuing need for the discovery of novel insecticides for crop protection, and in particular the need for those acting via novel modes of action prompted our investigation into a new series of indazoles. The target indazoles were designed based on pyrazoline models with known activity (1). At the outset of this work the pyrazoline mode of action was unknown, however, there were no commercial products from this class and the mode of action appeared to differ from conventional insecticides. Subsequently, Salgado reported these compounds acted via blockade of the sodium channel (2), a mode of action similar to that of local anesthetics, and confirmed our expectation that these represented a new site for insecticides.

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

Pyrazoline insecticides were first described by Wellinga, Mulder and Van Daalen in the early 70's (3-5). Analogs, such as PH 60-41, were found to have good lepidopteran activity. Further work showed that introduction of a 4-aryl substituent, as in PH 60-42, afforded compounds with a significant increase in potency. Jacobson later discovered that 4-carbomethoxy pyrazolines, such as RH-3421, were an interesting class with improved soil residual characteristics (6, 7). Other research groups described new pyrazoline insecticides containing novel substituents on the aryl and pyrazoline rings (8-15). In spite of their high levels of insecticidal activity it appears that pyrazolines failed to reach commercialization owing to a variety of issues associated with long environmental persistence, bioaccumulation and non-target toxicity (16, 17).



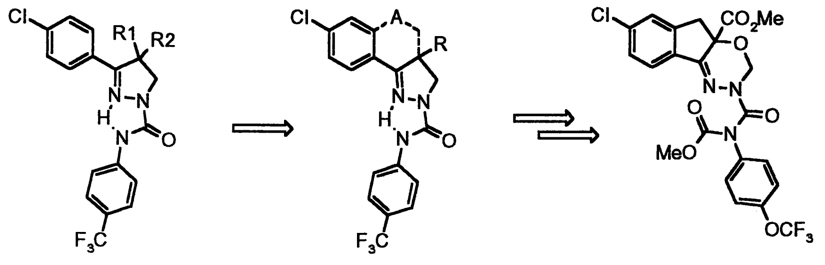
PH 60-41
Philips-DuPhar
1972

PH 60-42
Philips-DuPhar
1974

RH-3421
Rohm and Haas
1984

Figure 1: DuPhar and Rohm & Haas Pyrazolines

The indazole insecticides constituted our first step toward the new insecticide indoxacarb (Steward™, Avaunt™). X-Ray crystallographic data suggests that pyrazolines are relatively planar compounds owing both to extended π electron overlap and to an intramolecular hydrogen bond between the free NH and the 2-nitrogen of the pyrazoline ring. The 4-substituent of the pyrazoline ring extends out from this planar system. To effectively lock this confirmation we sought to append a tether between the ortho position of the 3-aryl group and the 4-position of the pyrazoline ring. Our initial targets were thus indazoles containing a two carbon link (A = CH_2). We extended this to include examples containing tethers where A was either oxygen or nitrogen.


Cl
R1
R2
N-N
H
N
O
F3C
A
R
CO2Me
O
N-N
O
O
MeO
N
OCF3

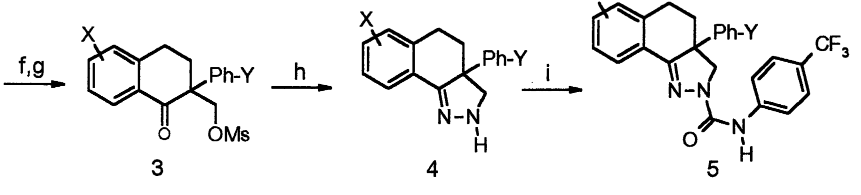
Pyrazolines

Indazoles (I)

Indoxacarb

Chemistry

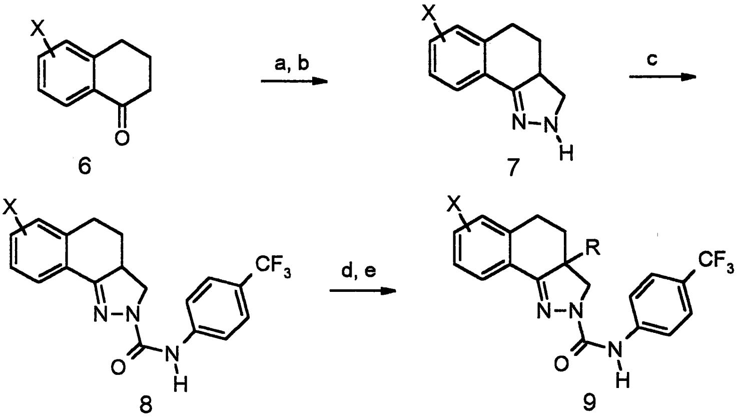
Indazoles containing an angular phenyl group were prepared as outlined in Scheme 1. Alkylation of substituted phenyl acetic esters with phenethyl bromides followed by conversion to the acid chloride and Friedel-Crafts cyclization afforded the intermediate 2-aryl tetralones **2**. Sequential treatment of the 2-aryl tetralone with formaldehyde and base followed by methanesulfonyl chloride afforded the corresponding mesylate **3**. Conversion of the mesylate to indazoles **5** was accomplished by reaction with hydrazine in refluxing n-butanol followed by treatment with an aryl isocyanate.


X
Br
+
Y
OEt
O
a, b, c
CO2H
X
Y
1
d,e
X
Ph-Y
O
2
f,g
X
Ph-Y
O
OMs
3
h
X
Ph-Y
N-N
H
4
i
X
Ph-Y
CF3
N-N
O
N
H
5

a.) NaH, DMF; b.) NaOH; c.) HCl; d.) $SOCl_2$, toluene, reflux; e.) $AlCl_3$, CH_2Cl_2; f.) CH_2O, NaOH; g.) $MeSO_2Cl$, Et_3N; h.) NH_2NH_2, n-BuOH, reflux; i.) CF_3-PhNCO

Scheme 1: Synthesis of angular substituted indazoles (R = Ph)

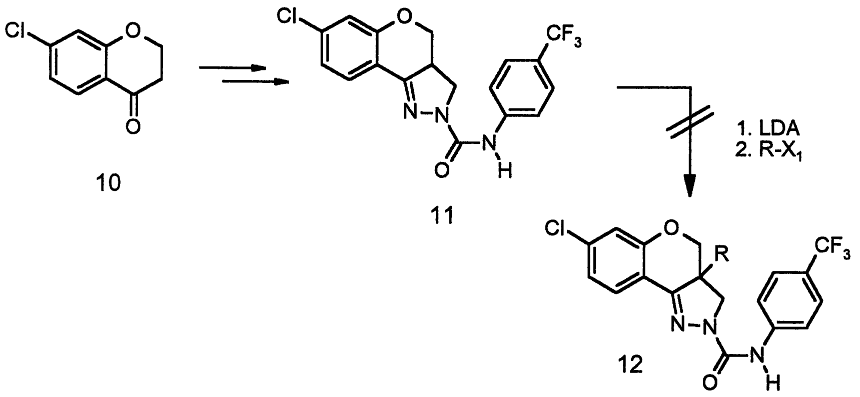
Indazoles containing an angular alkyl or ester group were prepared as outlined in Scheme 2 by a process similar to that described by Jacobson (6). Substituted tetralones were converted to the corresponding indazoles **7** by sequential Mannich reaction and hydrazine cyclization. Treatment of **7** with an aryl isocyanate afforded indazoles **8** with hydrogen at the angular position. Deprotonation of 8 with two equivalents of LDA and subsequent quenching of the dianion with electrophilic halides such as methyl iodide and methyl chloroformate afforded the angular substituted indazoles **9**.



a.) CH_2O, Me_2NH_2; b.) NH_2NH_2; c.) CF_3-PhNCO; d.) LDA (2eq); e.) R-X_1

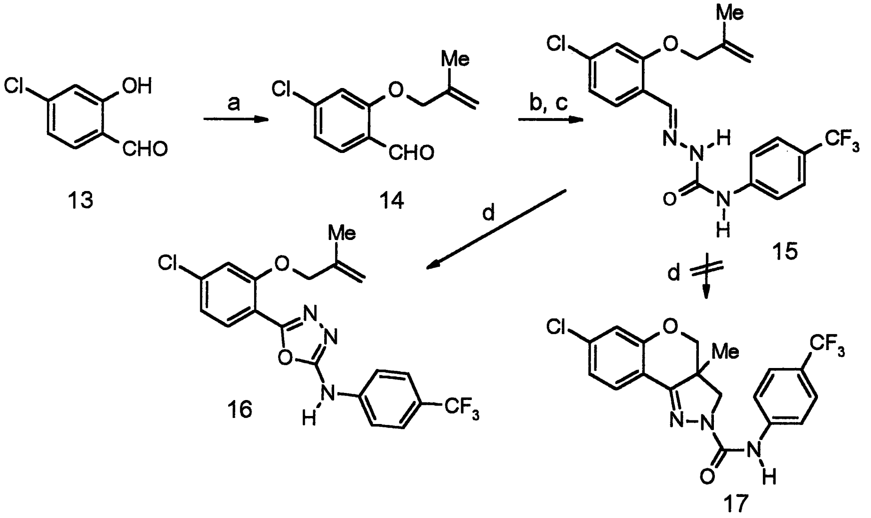
Scheme 2: Synthesis of indazoles via angular alkylation

Oxyindazole analogs (I, A = O) containing hydrogen at the angular position **11** were prepared from substituted chromanones in a manner similar to that described for the conversion of tetralones to indazoles (Scheme 3). However, direct angular alkylation failed under a variety of conditions to provide alkylated products **12**. We presume this problem was the result of a β-elimination of the chromanone oxygen upon deprotonation at the angular position, leading instead to decomposition products.


Cl
O
O
10
Cl
O
N-N
O
N
H
CF3
11
1. LDA
2. R-X1
Cl
O
R
N-N
O
N
H
CF3
12

Scheme 3: Attempted synthesis of target oxyindazoles via angular alkylation

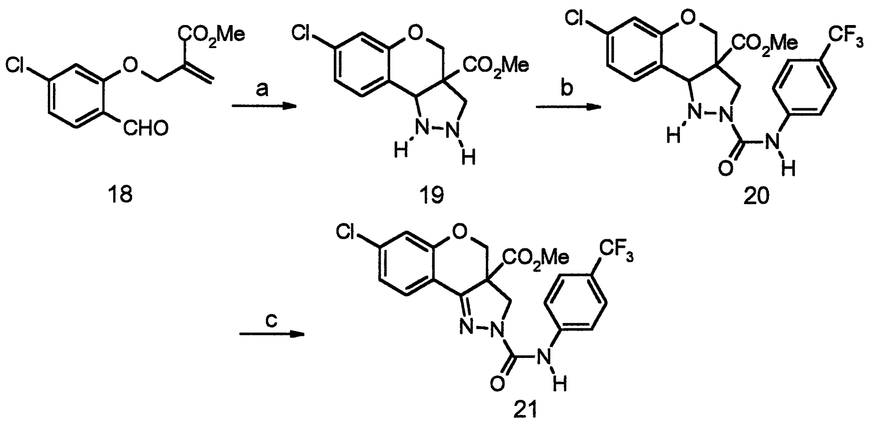
In order to circumvent this problem, we attempted to prepare oxyindazole **17** by a direct 3+2 intramolecular cyclization of semicarbazone **15** (Scheme 4). However, treatment of **15** with NBS and triethylamine produced instead oxadiazole **16** as a result of the competing intramolecular cyclization.


Cl
OH
CHO
13
a
Cl
O
Me
CHO
14
b, c
Cl
O
Me
N
N
H
O
N
H
CF3
15
d
d
Cl
O
Me
N
N
O
N
H
CF3
16
Cl
O
Me
N-N
O
N
H
CF3
17

a.) methallyl bromide, K_2CO_3, DMF; b.) hydrazine hydrate, EtOH, reflux; c.) 4-CF_3-PhNCO, EtOAc; d.) NBS, Et_3N

Scheme 4: Attempted synthesis of oxyindazoles via 3+2 cycloaddtion

The corresponding thermal reaction (Scheme 5) did ultimately prove successful albeit in low yield. Refluxing a mixture of aldehyde **18** with hydrazine hydrochloride in ethanol for several days provided the desired cycloadduct **19**. Reaction with aryl isocyanate followed by permanganate oxidation afforded the oxyindazole **21** in an overall yield of 3% from the aldehyde **18**. While the synthetic method was less than desirable the insecticidal activity proved to be exceptional and thus prompted a search for improved methods for angular substituted oxyindazoles.

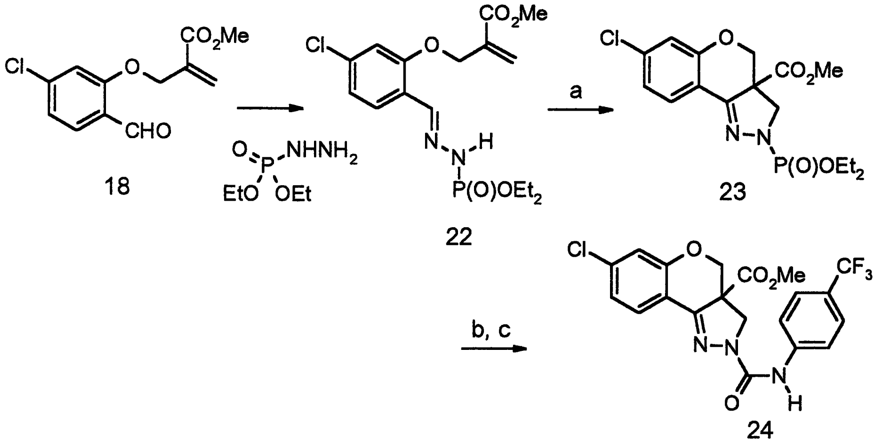


a.) hydrazine hydrate, EtOH, reflux; b.) 4-CF_3-PhNCO, EtOAc; c.) $KMnO_4$

Scheme 5: Synthesis of oxyindazoles via thermal 3+2 cycloaddition

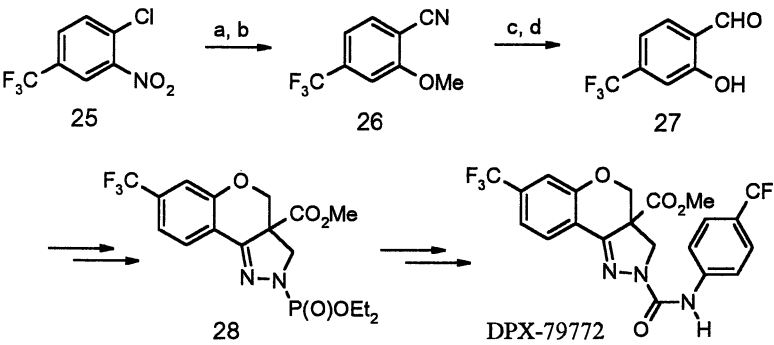
Incorporation of a phosporamide protecting group in the oxidative 3+2 cycloaddition proved to be the method of choice (Scheme 6). Treatment of phosphorus hydrazide **22** with NCS and triethylamine afforded the cycloadduct **23** cleanly and in high yield. Removal of the phosporus protecting group with HCl in methanol followed by reaction with aryl isocyanate afforded oxyindazole **24** in an yields generally in the range of 60-80% from aldehyde **18**.

This method was used to prepare a variety of substituted oxyindazoles including DPX-79772, the most active analog of this series. Synthesis involved preparation of 2-hydroxy-4-trifluoromethyl benzaldehyde **27** in four steps from the available 2-chloro-5-trifluoromethyl nitrobenzene **25** followed by the 3+2 cyclization route (Scheme 7).


CO2Me
Cl
O
CHO
18
O
P
NHNH2
EtO
OEt
22
N
N
H
P(O)OEt2
a
23
N-N
CO2Me
P(O)OEt2
b, c
24
CF3
N
H
O

a.) NCS, Et_3N; b.) conc. HCl, MeOH; c.) 4-CF_3-PhNCO, aq. K_2CO_3, EtOAc

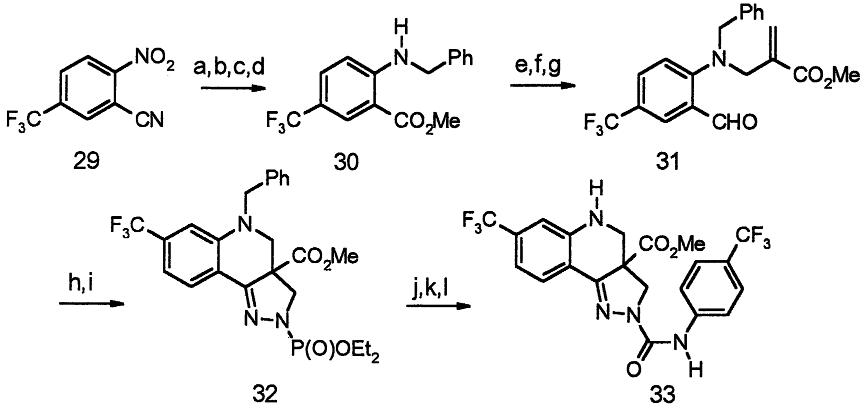
Scheme 6: Synthesis of oxyindazoles via oxidative 3+2 cycloaddition


Cl
F3C
NO2
25
a, b
CN
OMe
26
c, d
CHO
OH
27
F3C
O
CO2Me
N-N
P(O)OEt2
28
CF3
N
H
O
DPX-79772

a.) CuCN, DMF; b.) NaOMe, MeOH; c.) DiBAl-H; d.) LiCl, DMSO

Scheme 7: Synthesis of DPX-79772

Azaindazoles **33** were also prepared using the 3+2 cyclization strategy (Scheme 8). These analogs required protection of the free NH prior to cyclization. Reaction of **30** with 2-bromomethylacrylate followed by ester to aldehyde conversion afforded intermediate **31**. Conversion of **31** to the phosphorus hydrazide and subsequent treatment with NCS and triethylamine produced the cycloadduct **32** in good yield. Synthesis of the azaindazoles **33** was completed by removal of the phosphoramide group, reaction with aryl isocyanate and finally hydrogenolysis of the benzyl protecting group over palladium in formic acid.



a.) $TiCl_3$, HCl b.) NaOH c.) $SOCl_2$, MeOH d.) BnBr, K_2CO_3 e.) LAH; f.) MnO_2; g.)2-(CO_2Me)allyl bromide, NaH; h.) P(O)(EtO)$_2$NHNH$_2$; i.) NCS, Et_3N j.) HCl, MeOH; k.) 4-CF_3-PhNCO; l.) HCO_2H, Pd/C

Scheme 8: Synthesis of Azaindazoles

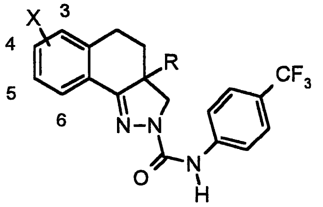
Insecticidal Activity

The insecticidal activity for indazoles is summarized in Table 1. The LC_{80} represents the lowest rate at which a minimum of 80% mortality was achieved across the rate range of 250, 100, 50, 10 and 2.5 ppm.

Entries (101-112) contrast structure-activity trends for a series of substituents X at the 3, 4 and 5 positions of the indazole. The following structure activity trends were observed:

- The X substituent generally followed the activity trend CF3, CF3CH2O > Cl, Br > H, F, > Me, OMe.
- The location of the X substituent is preferred at the 4-position.
- Substituents at the 3-position were typically less active, while substituents in the 5-position were inactive.
- Fluorine as the X substituent proved to be an exception with fluorine in the 3-position preferred over fluorine in the 4-position.

Table 1. Lepidopteran Activity of Selected Indazoles



			LC_{80} (ppm)	
Entry	*X*	*R*	*TBW*	*FAW*
101	H	CO_2Me	>250	100
102	3-F	CO_2Me	100	10
103	3-Cl	CO_2Me	>250	50
104	4-F	CO_2Me	>250	100
105	4-Cl	CO_2Me	250	10
106	4-Br	CO_2Me	100	2.5
107	4-CF_3	CO_2Me	2.5	2.5
108	4-OCH_2CF_3	CO_2Me	2.5	2.5
109	4-Me	CO_2Me	>250	250
110	4-OMe	CO_2Me	>250	>250
111	5-F	CO_2Me	>250	>250
112	5-Cl	CO_2Me	>250	>250
113	4-Cl	H	>250	50
114	4-Cl	Me	>250	50
115	4-Cl	Ph	2.5	10
116	4-Cl	4-F-Ph	2.5	10
117	4-Cl	4-Cl-Ph	50	50
118	4-Cl	4-Br-Ph	10	2.5

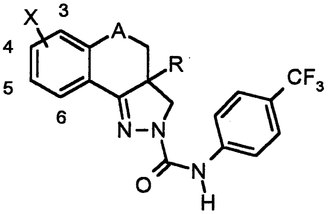
Note: TBW (Tobacco budworm, Heliothis virescens), FAW (Fall Armyworm, Spodoptera frugiperda)

Entries (105, 113–118) contrast structure-activity trends for a series of angular substituents R with the X substituent held constant as 4-Cl. The following structure-activity trends were observed:

- Compounds lacking angular substitution (R = H) were generally only weakly active or devoid of activity.
- Compounds containing alkyl groups at the angular position, while marginally better than hydrogen were moderately active at best.
- Angular substituents selected from phenyl, substituted phenyl and carbomethoxy generally provided the highest levels of activity consistent with literature precedence for pyrazoline substituents at the 4-position.

Insecticidal activity for selected oxyindazoles and azaindazoles is summarized in Table 2. These compounds represent some of the most potent analogs prepared and compare favorably with known pyrazoline standards (RH-3421 and PH 60-42) on both tobacco budworm and fall armyworm. The most active of these, DPX-79772 (entry 203) was evaluated in field trials across a broad spectrum of lepidoptera. Excellent crop protection was observed across the insect spectrum in a rate range of 30-125 g/Ha.

Table 2. Lepidopteran Activity of Selected Oxyindazoles and Azaindazoles



Entry	X	R	A	LC_{80} (ppm) TBW	FAW
201	Cl	CO_2Me	O	50	10
202	Cl	4-F-Ph	O	10	2.5
203	CF_3	CO_2Me	O	< 2.5	< 2.5
204	CF_3	CO_2Me	NH	2.5	2.5
205	CF_3	CO_2Me	NMe	50	10
PH 60-42	----	----	----	250	10
RH 3421	----	----	----	50	50

Note: TBW (Tobacco budworm, Heliothis virescens), FAW (Fall Armyworm, Spodoptera frugiperda)

In conclusion we have demonstrated that the pyrazoline spatial orientation can be constrained into a preferred confirmation for select substituent groups and that the resultant indazole, oxyindazole and azaindazole derivatives represent a new active class of insecticide. While these results did not solve all of the problems associated with soil persistence and/or bioaccummulation they did provide new insight into the geometric requirements for activity. This information was in turn crucial in the indoxacarb discovery.

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Chapter 12

1,3-Carbon–Nitrogen Atom Inversion: A Versatile Strategy for the Discovery of Novel Sodium Channel Blocking Insecticides

**Thomas M. Stevenson, Charles R. Harrison, Patrick D. Lowder,
Brett A. Crouse, Robert W. March, Martin J. Currie,
Milagro P. Folgar, and Dominic M. T. Chan**

Stine-Haskell Research Center, DuPont Agricultural Products, Building 300, Newark, DE 19714

We have previously disclosed that nitrogen atom inverted analogs of pyrazoline insecticides are insecticidal. We have now found that similar nitrogen atom inversion of oxyindazole, semicarbazone, pyridazine and oxadiazine insecticides also results in active compounds. These targets were synthesized by a number of different cycloaddition reactions. Carboxanilide versions of the oxyindazoles were made by an intramolecular nitrile-imine cycloaddition. Pyridazines were made by a hetero Diels-Alder reaction. The structure activity relationships found for these carboxanilides are very similar to those found for the traditional pyrazoline insecticides.

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

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Introduction

Previously we disclosed carboxanilide insecticides which were based on the concept of inverting the nitrogen atoms of the hydrazone substructure found in the pyrazolines (*1, 2*). Thus as seen in Figure 1. the target compounds **2** had the key carboxamide function attached via carbon instead of nitrogen found in the original pyrazolines **1**. The aryl ring traditionally found at C-3 was instead moved to N-1.

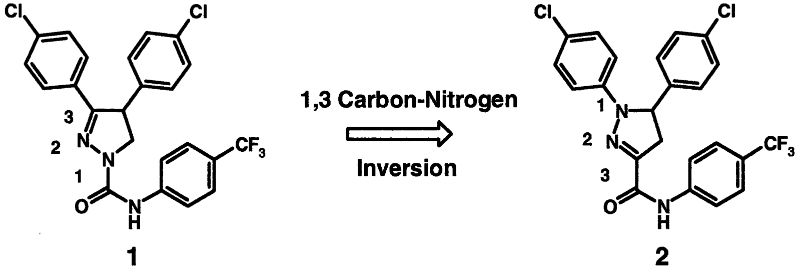
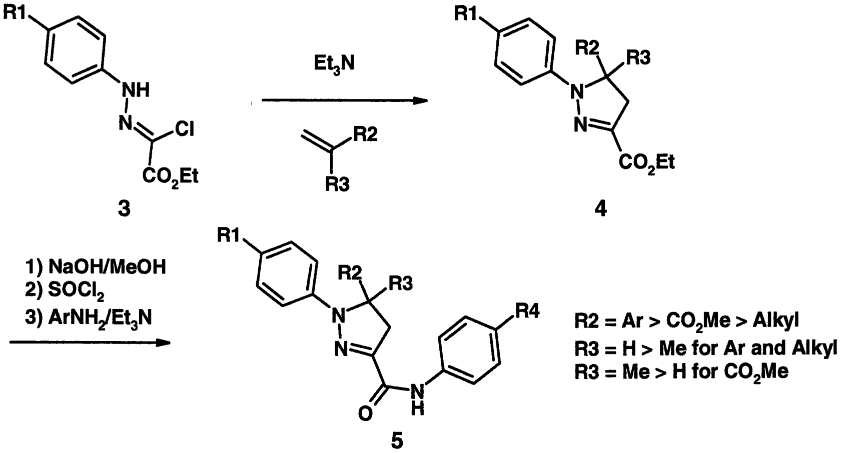

Cl
Cl
3
2
1
N
N
O
N
H
CF_3
1
1,3 Carbon-Nitrogen
Inversion
Cl
Cl
1
2
3
N
N
O
N
H
CF_3
2

Figure 1. Nitrogen-Carbon Atom Inversion leads to Pyrazoline Carboxanilides

These structures were made by a nitrile-imine cycloaddition of either methacrylates or styrenes as shown in Scheme 1. Both the dipolarophiles and the hydrazonyl chlorides **3** (precursors of the nitrile-imines) were readily available. The synthesis was very practical and over 1000 pyrazolines of structure **5** were prepared via pyrazoline esters **4**.

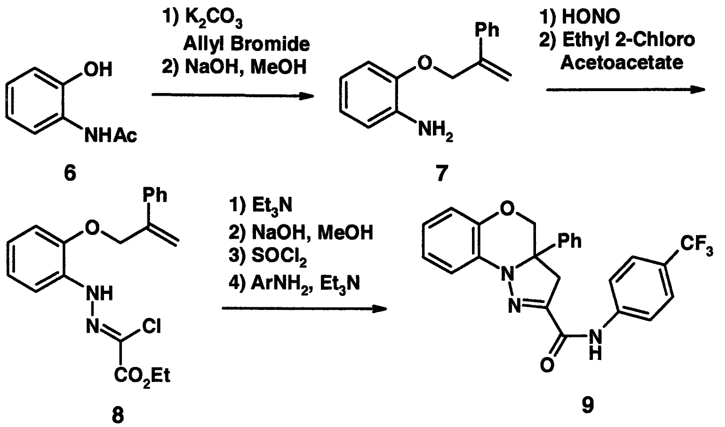

R1
NH
N
Cl
CO_2Et
3
Et_3N
R2
R3
R1
R2
R3
N
N
CO_2Et
4
1) NaOH/MeOH
2) $SOCl_2$
3) $ArNH_2/Et_3N$
R1
R2
R3
N
N
O
N
H
R4
5
R2 = Ar > CO_2Me > Alkyl
R3 = H > Me for Ar and Alkyl
R3 = Me > H for CO_2Me

Scheme 1. Analoging Strategy for Pyrazoline-3-Carboxanilides

The pyrazoline carboxanilides had very good activity, especially against Lepidopteran pests. The structure-activity relationships were very similar to known pyrazoline insecticides, but not exactly the same. The different synthetic route allowed us to easily challenge known structure-activity trends and make a much wider variety of R2 and R3 substituents than had been made in traditional pyrazolines. Of particular interest was the fact that when R2 was branched alkyl unexpectedly good activity was seen. Such key new learnings in structure-activity were directly applicable to DuPont's later programs in oxyindazoles (*3*), semicarbazones (*4*), pyridazines (*5*) and oxadiazines.

Conformationally Restricted Pyrazoline Carboxanilides

We also investigated intramolecular versions of our nitrile-imine cycloaddition reactions. Padwa and Garanti (*6,7*) had independently discovered that such cycloadditions were possible with ester substituted hydrazonyl chlorides with a pendant alkene. They had studied only simple alkenes, but we were confident that more complicated pendant alkenes would also undergo cycloaddition (Scheme 2). Our first attempts at cycloaddition began with an *ortho*-acetamidophenol **6**. We alkylated **6** with a phenyl-substituted allylic bromide. Deprotection with methanolic hydroxide gave the free amine **7** which was diazotized and coupled with ethyl 2-chloroacetoacetate to give cycloaddition precursor **8**. The hydrazonyl chloride **8** underwent smooth cycloaddition when treated with triethylamine. The tricyclic pyrazoline was hydrolysed and converted to the carboxanilide **9** via the acid chloride. This conformationally restricted analog of our carboxanilides showed good activity on lepidopteran species (*8*).



Scheme 2. Synthesis of a Conformationally Restricted Pyrazoline

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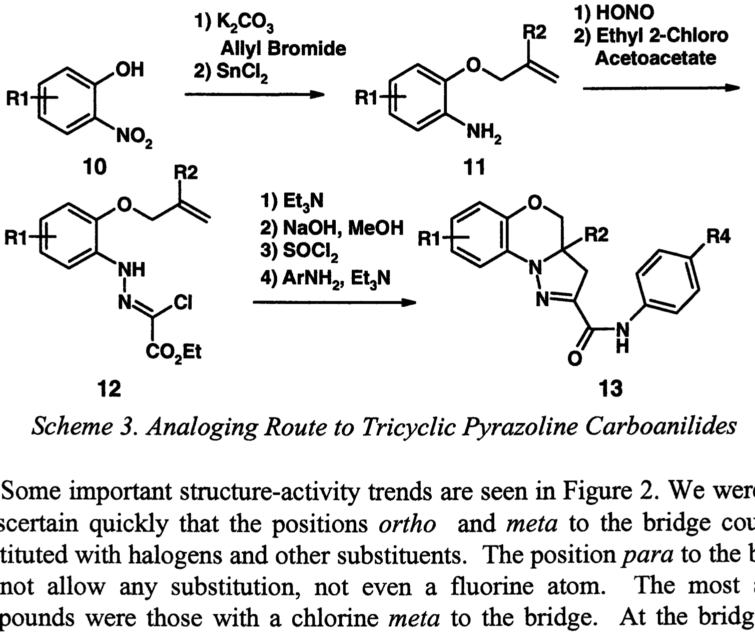
In order to find optimal substituents and substitution patterns we needed a more versatile synthetic method. Since there were a number of different o-nitrophenols available, we chose to use them as the starting materials for the analoging program as shown in Scheme 3. Etherification of the nitrophenols **10** was readily accomplished with a variety of allylic bromides using potassium carbonate as base in dimethylformamide. Reduction of the nitro group to give **11** without affecting the double bonds was conveniently carried out with tin chloride in either ethyl acetate or ethanol (*9*). Japp-Klingemann reaction of the anilines gave the hydrazonyl chlorides **12**. Cyclization as before was carried out in toluene with triethylamine. The intermediate esters were hydrolysed and converted to the anilides **13** without problems.



Scheme 3. Analoging Route to Tricyclic Pyrazoline Carboanilides

Some important structure-activity trends are seen in Figure 2. We were able to ascertain quickly that the positions *ortho* and *meta* to the bridge could be substituted with halogens and other substituents. The position *para* to the bridge did not allow any substitution, not even a fluorine atom. The most active compounds were those with a chlorine *meta* to the bridge. At the bridgehead postion a variety of substitutions retained activity. The most active compounds had either a 4-fluorophenyl or a methyl ester at the bridgehead. An optimal compound with a chlorine *meta* to the bridge, R2 as 4-fluorophenyl and R as trifluoromethoxy had activity against fall armyworm at 2.5 ppm and better residual activity than the monocyclic pyrazoline-3-carboxanilides. These results correlated well with those found for oxyindazole insecticides (*3*).

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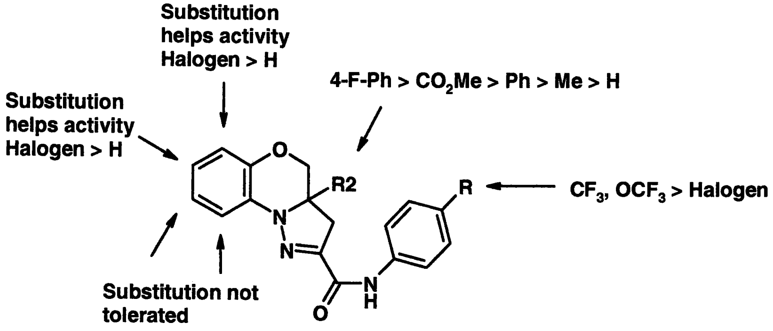
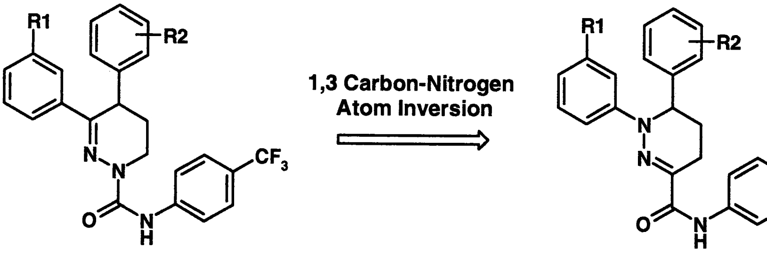

Substitution helps activity Halogen > H
Substitution helps activity Halogen > H
4-F-Ph > CO2Me > Ph > Me > H
R2
R
CF3, OCF3 > Halogen
O
N
N
N
H
O
Substitution not tolerated

Figure 2. Structure-Activity Trends for Tricyclic Pyrazoline Carboxanilides

6-Membered Heterocyclic Carboxanilides

When it was discovered that pyridazines **14** with a 3-*meta*-substituted aryl ring were highly active insecticides (*5*), we immediately turned our attention to carbon-nitrogen atom inverted pyridazines **15** (Figure 3).


R1
R2
N
N
CF3
O
N
H
1,3 Carbon-Nitrogen Atom Inversion
R1
R2
N
N
CF3
O
N
H

14 **15**

Figure 3. Pyridazine Carboxanilides

Synthetically, it appeared that nitrogen atom inverted pyridazines might be synthesized via a hetero Diels-Alder reaction (*10*). However, there was no literature precedent for cycloadditions with a heterodiene like **18** (Scheme 4). In fact, Curtin (*11*) had shown that a similar diene derived from alpha-bromoacetophenenone did not partcipate in cycloaddition reactions with isoprene. Nonetheless, we tried the reaction of ethyl bromopyruvate with phenylhydrazine in the presence of an excess of styrene and sodium carbonate. Presumably hydrazone **17** was formed and reaction with carbonate gave **18**, which underwent hetero Diels-Alder reaction to give a pyridazine, which was converted to carboxanilide **19**. The insecticidal activity of **19** prompted an analoging program (*12*).

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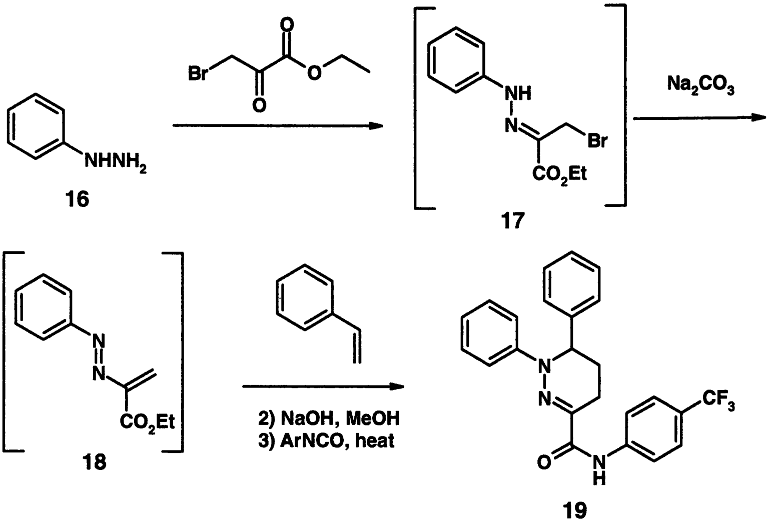
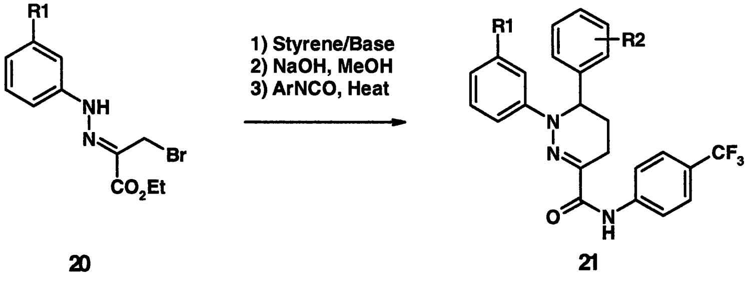

Br
O
O
O
NHNH$_2$
16
NH
N
Br
CO$_2$Et
17
Na$_2$CO$_3$
N
N
CO$_2$Et
18
2) NaOH, MeOH
3) ArNCO, heat
N
N
O
N
H
CF$_3$
19

Scheme 4. Synthesis of a Pyrdazine-3-Carboxanilide by Hetero Diels-Alder Reaction

As shown in Scheme 5, we began an analoging program and found that the reaction sequence was adaptable to other styrenes and phenyl hydrazines. However, as we changed to phenyl hydrazines with more strongly electron withdrawing groups such as 3-trifluoromethylphenyl hydrazine, we found that the hydrazones **20** became more stable and could often be isolated. Carbonate was unable to promote the formation of these heterodienes. Turning to the use of sodium hydride, we found that the heterodienes were formed and with styrenes gave cycloadducts which were converted to anilides **21** by standard methods.


R1
NH
N
Br
CO$_2$Et
20
1) Styrene/Base
2) NaOH, MeOH
3) ArNCO, Heat
R1
R2
N
N
O
N
H
CF$_3$
21

Scheme 5. Analoging Route for Pyridazine-3-Carboxanilides

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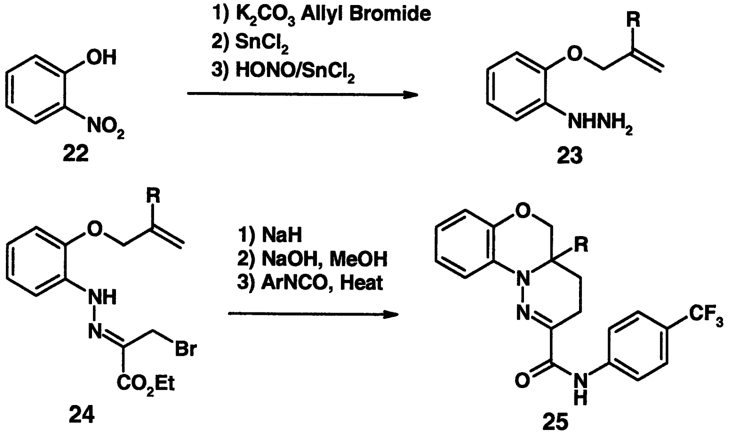
We found that it was also possible to carry out the cycloaddition process in an intramolecular fashion (Scheme 6). We synthesized a phenylhydrazine **23** containing a tethered alkene by alkylation of *ortho*-nitrophenol **22**. Reduction of the nitro compound and diazotization/reduction provided **23**. Condensation with ethyl bromopyruvate gave hydrazone **24** and treatment with sodium hydride gave the tricyclic pyridazine products in moderate yield. Conversion to the anilides **25** was straightforward.



Scheme 6. Intramolecular Hetero Diels-Alder Reactions

A related group of targets were oxadiazines. The oxadiazine nucleus contains a hydrolytically sensitive O-C-N linkage which could lead to more facile breakdown in the environment. We envisioned that these molecules might be made by cyclization of oxalic hydrazides **27** with dibromoalkanes as shown in Scheme 7. The initial hydrazides **27** could be made by the reaction of diethyloxylate with *meta*-substituted phenylhydrazines **26**. Reaction with ethyl oxalyl chloride or dimethyl oxalate gave very little desired material. Cyclization with excess 1,2-dibromoarylethanes and potassium carbonate proceeded in dimethylformamide at 100 ° C. An isomeric 6-phenyl oxadiazine **28** and the desired 5-substituted product **29** were isolated. Both were converted to anilides by Weinreb's method (*13*) with trimethylaluminum and 4-trifluoromethoxyaniline, but only 5-phenyloxadiazines **30** were active (*14*). We carried out the analoging program with a variety of readily available dibromostyrenes. The ratio of the 5- to 6-phenyloxadiazines was highly influenced by the electronics of the starting phenylhydrazine. Highest yields of 5-substituted products were obtained with phenylhydrazine and lowest yields with *meta*-trifluoromethylphenylhydrazine. Pyridylhydrazines gave only 6-substituted oxadiazines.

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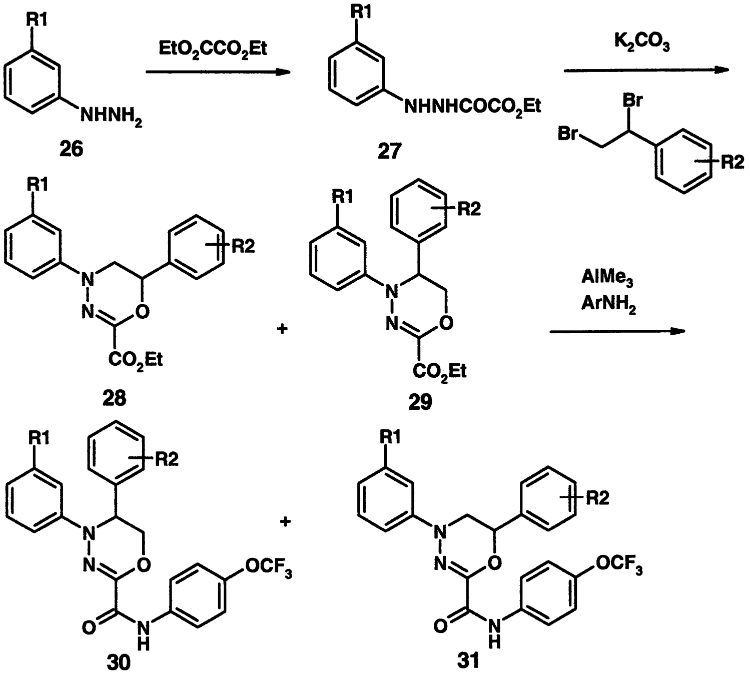

Scheme 7. Synthesis of 1,3,4-Oxadiazine-2-Carboxanilides

Alkyl substituted dibromides were also investigated. Cyclization of oxalic hydrazides **27** with 1,2-dibromopropane and 1,2-dibromobutane gave good yields of desired products. These cyclizations were less subject to electronic control and desired product was isolated in all of the series.

Structure-activity trends for the pyridazines and oxadiazines are shown in Figure 4. The aryl substitution pattern was as expected and the N-aryl group needed to have *meta*-substitution for activity. The C-aryl was optimally substituted at the *para*-position, but compounds with *ortho*- and *meta*-substitution retained some activity. Alkyl products retained activity, but had less activity on Lepidopteran insects and higher activity on Coleopteran and Homopteran insects than their phenyl counterparts. An optimal compound with R1 as trifluoromethyl, R2 as 4-fluorophenyl, Q as oxygen and R as trifluoromethoxy was active at between 2.5 and 10 ppm on fall armyworm and tobacco budworm with good residual activity. A compound with the same substituents, but with R2 as ethyl had activity on southern corn rootworm larvae at 2.5 ppm, aster leafhopper at 100 ppm, and fall armyworm at 50 ppm.

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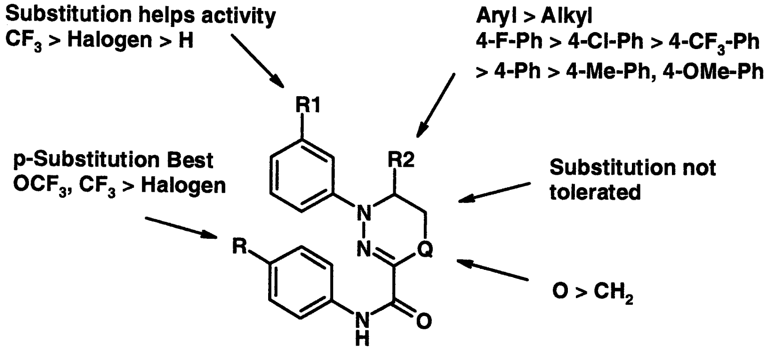
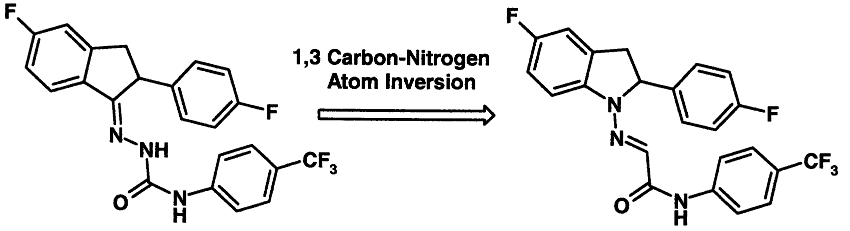

Substitution helps activity
CF3 > Halogen > H
Aryl > Alkyl
4-F-Ph > 4-Cl-Ph > 4-CF3-Ph
> 4-Ph > 4-Me-Ph, 4-OMe-Ph
R1
R2
p-Substitution Best
OCF3, CF3 > Halogen
Substitution not tolerated
R
N
N
Q
O > CH2
N
H
O

Figure 4. Structure-Activity Trends for 6-Membered Ring Carboxanilides

Aminoindoline Carboxanilides

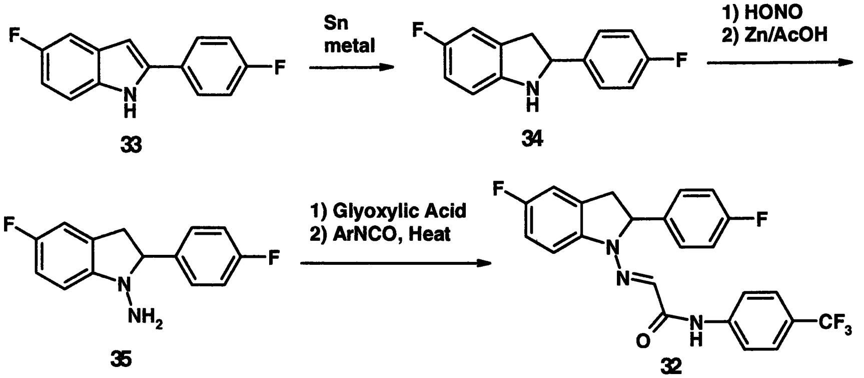
Nitrogen atom inverted analogs of the semicarbazone insecticides **32** (*4*) were also investigated. Target molecules such as **33** are derived from indolines as opposed to ketones for the traditional semicarbazones (Figure 5.).


F
F
N
NH
O
N
H
CF3
1,3 Carbon-Nitrogen Atom Inversion
F
N
F
N
O
N
H
CF3

32 **33**

Figure 5. Carbon-Nitrogen Atom Inversion of Semicarbazones leads to N-Aminoindoline Hydrazones as Targets

Retrosynthetically, the nitrogen atom inverted analogs require a synthesis of indolines and then an amination reaction. In order to synthesize the 2-arylindolines **34** required for optimal analogs we began with 2-arylindoles **33** as shown in Scheme 8. These could be reduced by elemental tin to give the indolines **34**. N-Amination was unsuccessfully approached first with hydroxylamine-O-sulfonic acid. We turned to a more traditional two step amination. Nitrosation of the indoline was followed by a reduction with zinc in acetic acid to obtain the required N-amino-2-arylindoline **35** (*15*). Hydrazone formation was carried out with glyoxylic acid. The acids were converted directly to the target amides such as **32** by reaction with arylisocyanates. Anilide **32** had activity on Fall Armyworm and Tobacco Budworm between 10-50 ppm. This sequence was also applicable to alkyl substituted indoles.



Scheme 8. Synthesis of a Nitrogen Atom Inverted Semicarbazone

The carbon-nitrogen atom inverted semicarbazones had good activity as insecticides (*16*). The structure activity trends were also similar to traditional semicarbazones. The hydrazones derived from glyoxylic acid were all active, but moving to pyruvic acid derived hydrazones gave compounds which were practically devoid of activity. The stongest activity for the aminoindoline derived carboxanilides was on Lepidopteran pests for 2-aryl compounds and Coleopteran pests for 2-alkyl compounds, mirroring the results from semicarbazones.

Conclusions

Programs based on nitrogen atom inversion played an important role in the development of Indoxacarb. The different starting materials and synthetic routes used for nitrogen atom inverted targets and traditional targets led us to investigate a larger group of substituents and substitution patterns than either program could have afforded individually. Structure-activity surprises were quickly incorporated into the other program. By carrying out the two programs simultaneously we were able to progress more rapidly through the arduous process that led ultimately to the important new Lepidopteran insecticide Indoxacarb.

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Chapter 13

Synthesis and Bilogical Activity of Semicarbazone Insecticides

George P. Lahm, Renee M. Lett, Jeffrey K. Long*, Patrick D. Lowder, Thomas M. Stevenson, Martin J. Currie, Milagro P. Folgar, Sandra M. Griswold, Margaret A. Lucas, Robert W. March, and Wendy A. March

Stine-Haskell Research Center, DuPont Agricultural Products, P.O. Box 300, Newark, DE 19714

N-Aryl semicarbazones of substituted indanones, tetralones, coumaranones, chromanones, and thiochromanones were prepared to investigate novel structures related to pyrazoline insecticides. These compounds were found to be potent agents for control of arthropod pests, particularly Lepidoptera and Coleoptera.

In the course of research related to the pyrazoline insecticides and the eventual discovery of indoxacarb (Steward™, Avaunt™), a variety of chemical structural types were investigated for their potential as sodium channel-active insecticides. As described in an earlier chapter of this book on indazole insecticides, substituted tetralones were prepared as precursors to aryl pyrazolines in which the pyrazoline ring and aromatic ring were tethered by a two-atom chain. We recognized that this added ring might favorably position substituent groups such that the overall molecular shape would imitate that of the indazole-type pyrazolines, even if the pyrazoline ring itself were not present.

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

To test this idea, tetralones **1**, prepared as intermediates to indazoles, were used to prepare N-aryl semicarbazones **2** as in Figure 1.

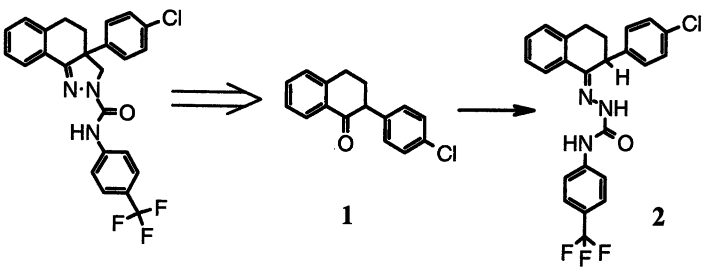
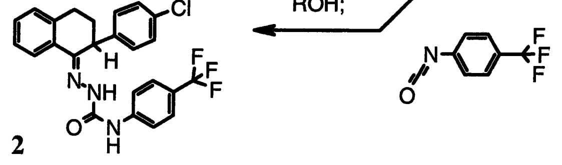

Cl
N·N
O
HN
F
F
F
O
Cl
1
Cl
H
N
NH
HN
O
F
F
F
2

Figure 1. Conceptual relationship of indazoles and semicarbazones

The first of these compounds **2** was active on southern corn rootworm, confirming the potential for the semicarbazones to be insecticidal.

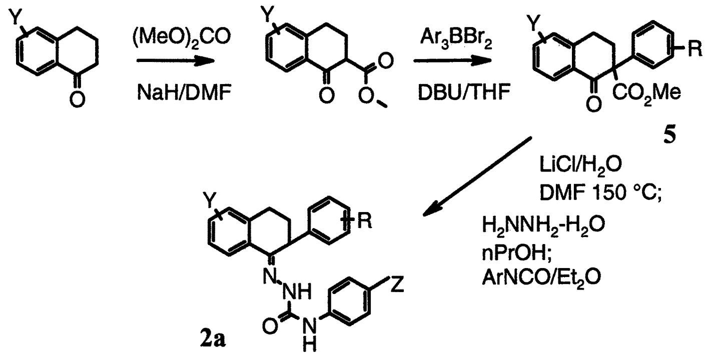
Chemistry

Tetralones were prepared by two major routes. The first utilized a strategy of alkylation of phenylacetates followed by Friedel-Crafts acylation, as in the preparation of **2** from **3** and **4** (*Scheme 1*).


O
O
Cl
Ph
Br
NaH/DMF
O
O
Cl
3
NaOH;
SOCl2;
AlCl3
O
Cl
4
H2NNH2-H2O
ROH;
N
O
F
F
F
Cl
H
N
NH
O
N
H
F
F
F
2

Scheme 1: Preparation of tetralone semicarbazones

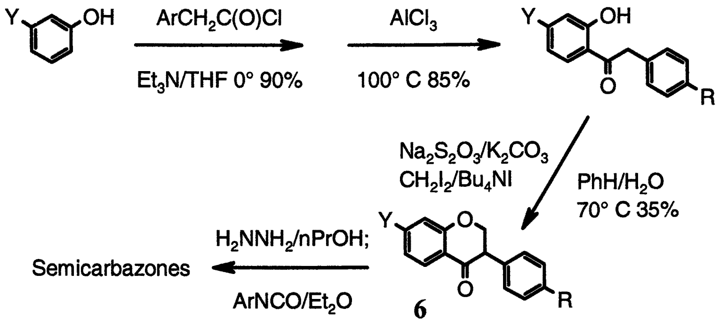
In an alternative approach, tetralones were converted to ketoesters, permitting the use of bismuth arylation chemistry (*1*) to obtain **5** (*Scheme 2*).


Y
(MeO)$_2$CO
NaH/DMF
O
Y
O
O
O
Ar$_3$BBr$_2$
DBU/THF
Y
R
O
CO$_2$Me
5
LiCl/H$_2$O
DMF 150 °C;
H$_2$NNH$_2$-H$_2$O
nPrOH;
ArNCO/Et$_2$O
Y
R
N
NH
O
N
H
Z
2a

Scheme 2: Bismuth arylation route to tetralones

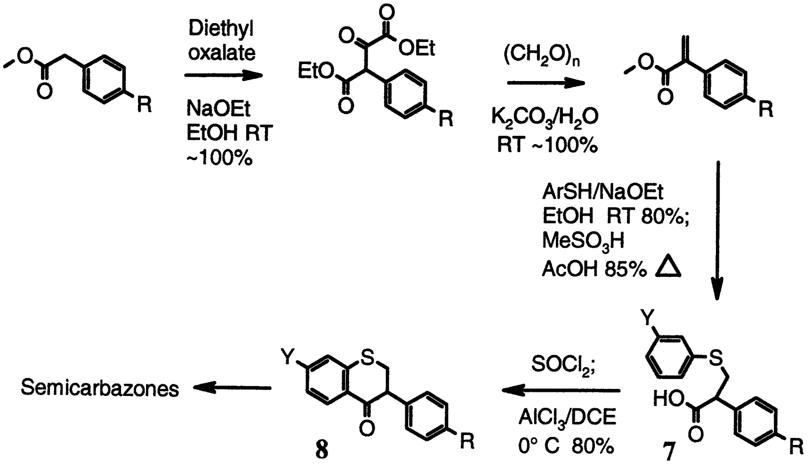
Although formation of hydrazones from ketones is often readily accomplished in hot ethyl alcohol, the 2-aryltetralones required higher-temperature reaction conditions, so 1-propanol or 1-butanol were often used as solvents in this step.

Concurrent work on oxyindazole analogs of pyrazolines indicated greater activity for compounds with a heteroatom in the ring tethering the pyrazoline to the aromatic ring, so we made chromanones to test whether their semicarbazones might also have enhanced efficacy. The chromanones **6** were prepared via Fries rearrangement and methylenation.


Y
OH
ArCH$_2$C(O)Cl
Et$_3$N/THF 0° 90%
AlCl$_3$
100° C 85%
Y
OH
O
R
Na$_2$S$_2$O$_3$/K$_2$CO$_3$
CH$_2$I$_2$/Bu$_4$NI
PhH/H$_2$O
70° C 35%
Y
O
O
R
6
H$_2$NNH$_2$/nPrOH;
ArNCO/Et$_2$O
Semicarbazones

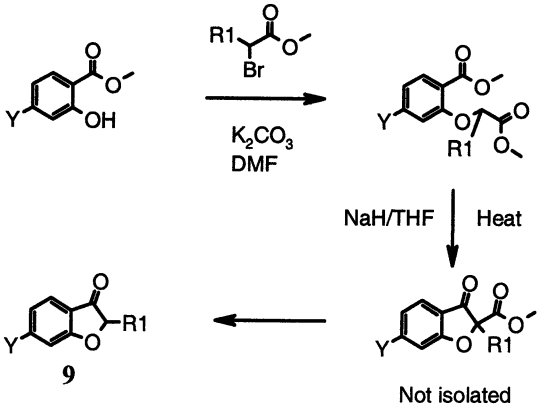
Scheme 3: Preparation of chromanones

Preparation of thiochromanones **8** was similar to that of the chromanones **6**, except that methylenation and Michael addition of a thiol were performed before Friedel-Crafts chemistry (*Scheme 4*). Hydrolysis of the ester group to obtain acids **7** was performed under acidic conditions to avoid a retro-Michael reaction. Friedel-Crafts acylation and standard handling of the resultant ketone afforded the desired semicarbazone products.


Diethyl oxalate
NaOEt
EtOH RT
~100%
OEt
EtO
R
$(CH_2O)_n$
K_2CO_3/H_2O
RT ~100%
ArSH/NaOEt
EtOH RT 80%;
$MeSO_3H$
AcOH 85% Δ
Y
S
HO
7
$SOCl_2$;
$AlCl_3/DCE$
0° C 80%
Semicarbazones
8

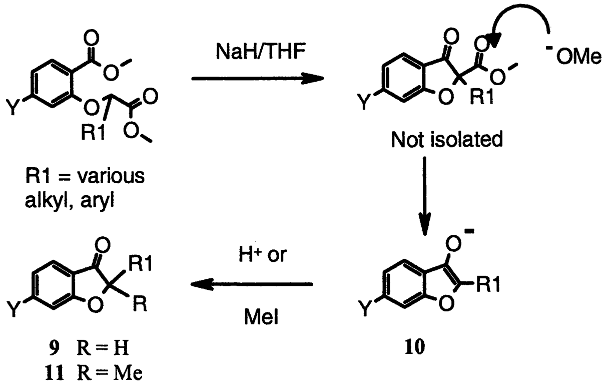
Scheme 4: Thiochromanone preparation

Smaller ring sizes were also of interest in this area, leading to the investigation of benzofuranones (coumaranones) **9** (*Scheme 5*).


R1
Br
K_2CO_3
DMF
Y
OH
NaH/THF
Heat
9
Not isolated

Scheme 5: Preparation of 2-substituted coumaranones

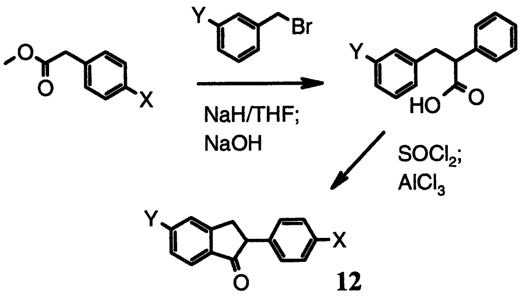
Under the conditions of this Dieckmann reaction, the ester group is lost, likely forming dimethyl carbonate (*2*). This suggests considerable stability and low reactivity of the resultant coumaranone anion, which could be viewed as the anion of a 3-hydroxybenzofuran, **10**. The anion can, however, be alkylated with iodomethane to prepare 2-methylfuranones **11** (*Scheme 6*).



Scheme 6: Formation of decarboxylated coumaranones

In most cases in which R1 was an aromatic group, only 2-methylfuranones **11** (containing a quaternary center) were successfully converted to semicarbazones by standard procedures. We expect that the corresponding intermediates **9** likely existed as the enol (hydroxybenzofuran) tautomers and were resistant to conversion to semicarbazones.

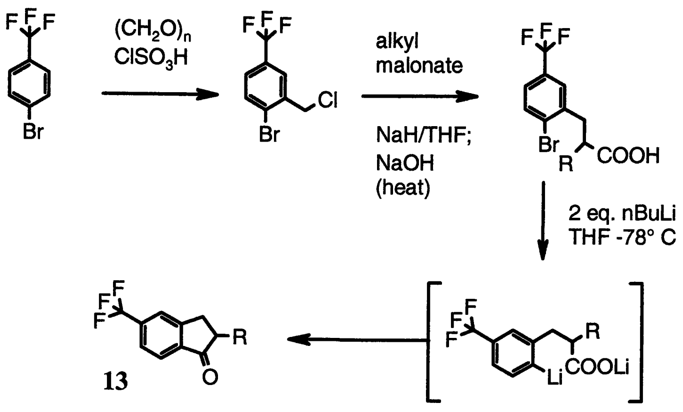
Indanones **12** were also targeted as ketone substrates early in this project. The first examples were prepared by alkylation of phenylacetates and cyclization using Friedel-Crafts conditions (*Scheme 7*).



Scheme 7: Preparation of 2-Arylindanones

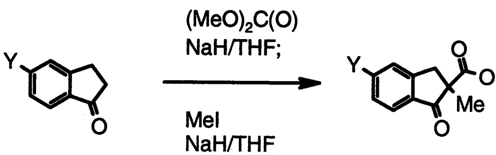
Semicarbazones of 2-substituted indanones proved to be quite active, which spurred us to make this our largest area of research on insecticidal semicarbazones. Thus, a variety of synthetic approaches to indanones were employed to accommodate different substitution patterns.

Oxyindazoles with a trifluoromethyl substituent on the aromatic ring were potent insecticides (see earlier indazole chapter of this book), so we particularly desired indanones with this substitution. However, CF_3 groups generally undergo undesired side reactions under Friedel-Crafts conditions, and our other methods of indanone preparation, mostly electrophilic cyclizations, were not successful with this strongly electron-withdrawing group. However, the method of Parham (*3*) was successfully employed to make the indanones **13**.



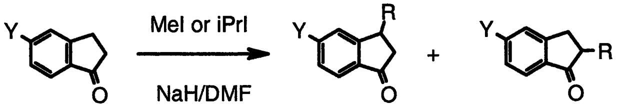
Scheme 8: Preparation of trifluoromethylindanones

Commercially available indanones were functionalized by several routes. Acylation with dimethylcarbonate and optional further alkylation provided ester-substituted indanones **14**.



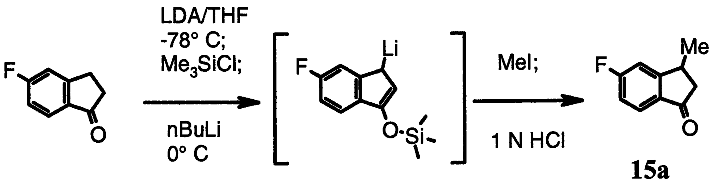
14

Saponification of the esters **14** provided 2-alkylindanones. We attempted to prepare 2-indanones by direct alkylation of the ketones, and found that we obtained 3-alkylindanones as well (see *4*). Use of excess sodium hydride as base in alkylation of 5-haloindanones led to the formation of the 3-alkylindanones **15** as well as the 2-alkylindanones **16**.



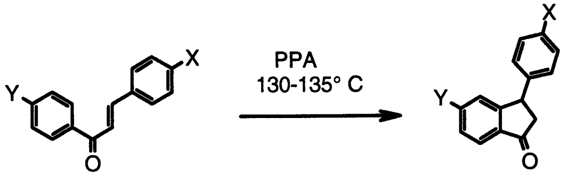
15 **16**

The route below cleanly accomplished this reaction, providing only the 3-alkyl regioisomer **15**. Formation of the silyl enol ether and deprotonation formed a benzo-cyclopentadienyl anion that reacted selectively at the 3-position (*5*). *In situ* hydrolysis of the enol ether afforded the product in a one-pot procedure.



15a

Good activity of the 3-alkylindanone semicarbazones inspired us to pursue 3-arylindanones **17**. These were prepared by the known Nazarov-style cyclization (*6*) of the readily available chalcones.



17

This successful use of the Nazarov cyclization also led us to explore it as a route to other indanones, for which it proved to be particularly effective.

Preparation of the Nazarov precursor **18** was readily accomplished by Friedel-Crafts reaction of halobenzenes followed by methylenation under a choice of standard conditions. Reaction of compounds **18** in sulfuric acid (*7*) afforded the desired indanones in high yield.

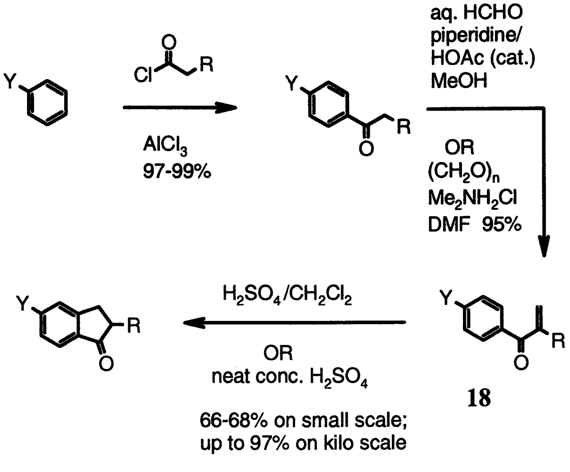
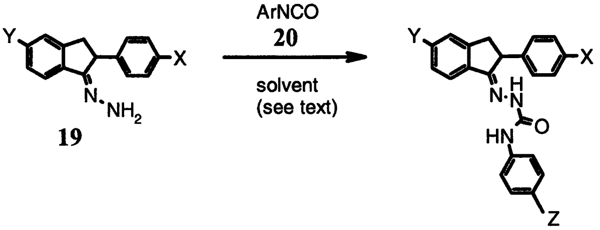
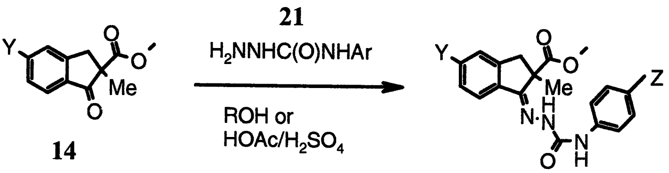

Y
Cl
O
R
AlCl$_3$
97-99%
aq. HCHO
piperidine/
HOAc (cat.)
MeOH
OR
(CH$_2$O)$_n$
Me$_2$NH$_2$Cl
DMF 95%
18
H$_2$SO$_4$/CH$_2$Cl$_2$
OR
neat conc. H$_2$SO$_4$
66-68% on small scale;
up to 97% on kilo scale

Figure 9: Nazarov preparation of indanones

In general, indanones were readily converted to the final semicarbazones under milder conditions than needed for the tetralone semicarbazones. The indanones reacted readily with hydrazine (hydrate) in refluxing ethanol, and the resultant hydrazones **19** reacted with a variety of aryl isocyanates **20** in aprotic solvents such as ether, tetrahydrofuran, or toluene.


Y
X
N
NH$_2$
19
ArNCO
20
solvent
(see text)
H
N·N
O
HN
Z

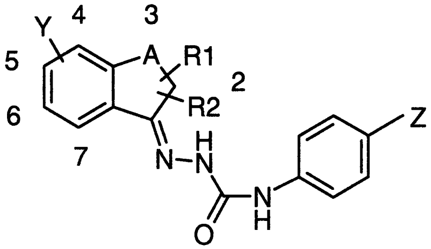
However, for indanone substrates such as the esters **14**, an alternate approach was necessary to avoid side-reactions of the ester group. Condensation of the ketone in alcohol or acetic acid with a pre-formed semicarbazide **21** (prepared by reaction of hydrazine with aryl isocyanates in toluene or ether) was successful in these cases.


Y
O
Me
14
21
H$_2$NNHC(O)NHAr
ROH or
HOAc/H$_2$SO$_4$
Z
N·N
H
O
N
H

Reaction of ketones with pre-formed semicarbazides was also advantageous on larger scale, due to the stability of the ketones and semicarbazides. Isolated hydrazone intermediates that were convenient to use on a research scale tended to form azines on larger scale, affecting the purity of the final products.

Insecticidal Activity

General trends in the activity of the semicarbazones were consistent with those of the pyrazolines and indazoles, with some differences specific to the semicarbazones. We observed these generalizations for semicarbazones prepared from different types of ketone substrates:

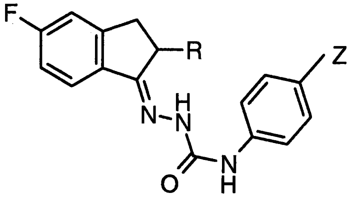


- Indanones (A = CH_2) provided the most active compounds against Lepidoptera and Coleoptera, with coumaranone types (A = O) also being quite effective, especially on Coleoptera.
- A single substituent was favored at the 2-position (R2 = H).
- The best R1 groups for Lepidopteran activity were haloaryl, aryl, and various branched and unbranched alkyls (isopropyl, propyl, and isobutyl).
- Small alkyl groups (especially methyl) provided excellent activity on Coleoptera. Ester groups afforded only modest activity on Coleoptera and low activity on Lepidoptera, in contrast to the indazoles and indoxacarb.
- Substitution at the 5-position of indanones and the equivalent position in other substrates was optimal, with the 4-position also giving good activity. The best substituents Y were halogens, nitrile, and to a lesser extent haloalkoxy and trifluoromethyl.
- Substitution of the N-aryl group of the semicarbazones followed the trends of the pyrazolines and indazoles, providing the best activity for Z = CF_3 and OCF_3, and good activity for Z = bromo and $OCHF_2$, all at the *para*-position of the phenyl ring.

The most-active semicarbazones were evaluated in field trials, and they showed levels of insect control competitive with commercial standards on selected species of insects.

Compound **22** controlled Colorado potato beetle at field rates of 5-10 g/Ha and boll weevil at 75-100 g/Ha, but did not control Lepidoptera well.

Compound **23** provided excellent plant protection and controlled Lepidopteran pests such as tobacco budworm (*Heliothis virescens*) and fall armyworm (*Spodoptera frugiperda*) at field rates of 28-56 g/Ha and 84-112 g/Ha, respectively.



22 R = CH_3, Z = CF_3

23 R = *p*FPh, Z = OCF_3

Conclusions

In conclusion, we found that semicarbazones of cyclic ketones were potent insecticides, similar to pyrazolines in their favored substitution patterns and symptomology of action, although more selective in spectrum of activity. These compounds also shared some of the problems of pyrazolines in soil persistence and/or bioaccumulation, although selected compounds demonstrated favorable properties in these regards, albeit generally with attenuated efficacy.

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Publication Date: July 29, 2001 | doi: 10.1021/bk-2002-0800.ch014

Chapter 14

N-Substituted Pyrazoline-Type Insecticides

Dominic M. T. Chan, Thomas M. Stevenson, David W. Piotrowski, Charles R. Harrison, Mohammed A. H. Fahmy, Rebecca L. Lowe, Kevin L. Monaco, Bonita M. Reeves, Milagro P. Folgar, and Elizabeth G. Esrey

Stine-Haskell Research Center, DuPont Agricultural Products, S300, P.O. Box 30, Newark, DE 19714–0030

Substitution on the urea nitrogen of insecticidal pyrazoline-type insecticides was explored as an approach to enhance environmental degradation, reduce bioaccumulation, and improve efficacy. The synthesis, biological activity, and molecular structure of these N-substituted pyrazolines and analogous systems are discussed.

The development of highly efficacious insecticides based on the original Philips-Duphar N-arylcarbamoylpyrazoline structure (*1, 2*) has been the subject of intense focus of DuPont Crop Protection for some time. In the course of our investigation, a number of novel structural motifs, e.g., indazoles, carboxanilides, and semicarbazones, with promising activity have been uncovered (*3,4,5*). Many of these compounds exhibit very good initial and residual control of lepidoptera and coleoptera. However, we recognize that pyrazoline-type insecticides have a number of shortcomings that need to be addressed before they can become viable candidates for commercial venture. In general, these analogs lack overall efficacy and spectrum. They also pose potential hurdles with registration since these compounds tend to have long soil persistence (*6*), as well as problems with bioaccumulation in mammalian tissues.

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

Finally, there is also evidence that some pyrazolines have relativity low photostability, which can adversely affect their performance in the field (7).

Objectives and Approach

The main focus of this project was to identify pyrazoline-based analogs which can address some or all of the shortcomings described above. Other objectives were to develop interesting chemistry and useful synthetic technology, as well as pertinent SAR information that we could use to guide us in the design of compounds that would ultimately lead to a candidate for commercialization.

The approach we took was to introduce a substituent on the urea nitrogen of the aromatic moiety as exemplified for the diaryl pyrazoline in Figure 1. It should be noted that our initial goal was not specifically to design a pro-insecticide, i.e., these N-substituted analogs would have inherent activity, although we were keenly aware that this mode of action could be operative once the compound was applied to the targeted insects. Nonetheless, we reasoned that a judicious choice of this substituent would allow us to fine-tune/optimize the physical properties and chemical behavior of the molecule. Thus, the analog may have spectral properties which render it more stable photolytically. The solubility of the compound could also be modified to aid formulation. The activity of the molecule could be further enhanced due to optimized lipophilicity. In addition, improved soil degradation and mammalian metabolic clearance could also be realized without sacrificing efficacy if the substituent were designed to allow selective decomposition of the molecule in soil and mammalian tissue, yet be readily removed *in vivo* by the insect to produce the parent pyrazoline as depicted in Figure 2. As an added bonus, the N-substituted analogs offer new synthetic opportunities which could ultimately lead to more efficient process development needed for commercial production.

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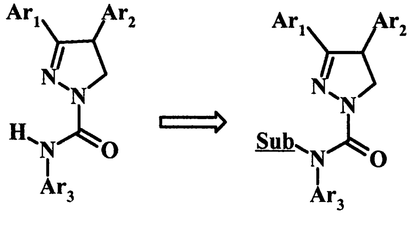

Sub:

Alkyl	e.g. CH_3, allyl, longer chains
Acyl	e.g. $COCH_3$, CO_2CH_3, $CONH_2$, $COCO_2R$
Aryl	e.g. Ph, C_6H_4X
Thio	e.g. SCO_2R, $SNR'CO_2R''$
Amino	e.g. NH_2, NHCOR

Figure 1. N-Substituted pyrazoline approach.

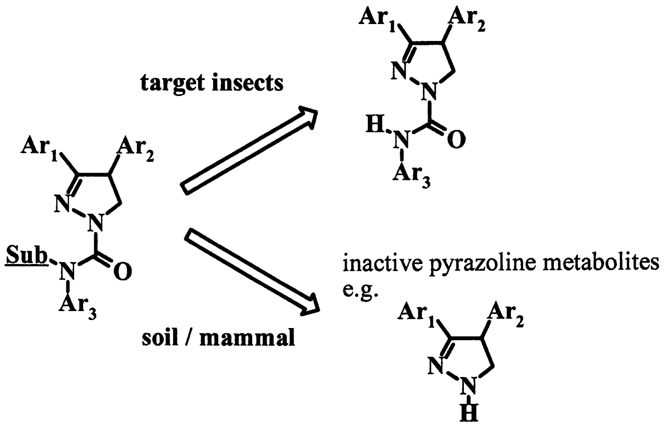

Figure 2. N-substituted pyrazoline as potential pro-insecticide.

The types of substitution that will be discussed in this chapter include acyl (acetyl, carboalkoxy, and oxalyl), alkyl, aryl, thio, and amino derivatives.

Synthesis of Analogs

Two general routes were developed for the synthesis of these N-substituted analogs as exemplified by the 3-arylpyrazoline in Figure 3: (*A*) direct substitution of parent N-H compound by deprotonation followed by quenching of the nitrogen anion by an appropriate electrophile, and (*B*) coupling of a pyrazoline precursor with a N-substituted carbamoyl chloride.

Both methods have their strengths and weaknesses. Approach *A* takes advantage of the ready availability of existing compounds from our various programs, although the strong base (NaH in most cases) needed for the deprotonation step could cause decomposition of the molecule in some instances. Approach *B* represents a more convergent route although the preparation of the requisite carbamoyl chloride could be a challenge.

N-Acetylated Analogs

One of the first analog groups we investigated was the acylated 1-carbamoyl-3,4-diaryl-pyrazolines. Thus, treatment of the pyrazoline precursor **1** with NaH in THF followed by the addition of acetyl chloride gave the acetylated

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product **2** (Figure 4). Both compounds **1** and **2** have similar spectrum and activity in our greenhouse tests with control of fall armyworm (FAW) at 1 ppm and boll weevil (BW) at 10 ppm. However, the acetylated pyrazoline **2** outperforms its parent compound **1** in field trials. Part of this superior performance can be attributed to a 20 nm decrease in the absorption maximum going from the parent N-H compound to the N-acyl compound **2**. This hypsochromic shift could impart improved photostability resulting in superior field performance.

Acetylation of the carboxanilide **3** in the same fashion produced the N-acetylated analog **4** (Figure 4). Interestingly, acetylation in this case causes a bathochromatic shift of 17 nm of the absorption maximum. In addition, no improvement of spectrum and activity was observed with compound **4**.

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N-Carboalkoxy Pyrazolines

The N-carbomethoxy pyrazoline **5** can be readily prepared from the coupling of the pyrazoline **6** with the carbamoyl chloride **7**. Comparison of the x-ray structures of **5** with the corresponding N-H compound **8** suggests that no conformational perturbation occurs upon the introduction of a CO_2Me function (*8*). As with the previous case of the acetylation of **1**, a hypsochromic shift in λ_{max} is observed with the carbomethoxylation (Figure 5).

Compound **5** shows similar efficacy against FAW and tobacco budworm (TBW) in greenhouse studies when compared to the parent N-H compound **8**. In various field trials, **5** controlled lepidopteran populations in leafy vegetables and corn at use rates of 25-100 g ai/ha, and was also effective against TBW, cabbage loopers, and beet armyworm in cotton down to 50 g ai/ha. The pyrazoline **5** also has a favorable aquatic safety and toxicity profile, with an added advantage of lower acute toxicity in mice than the parent compound **8**, e.g., ALD (approximate lethal dose) of **5** = 300 mg/kg, ALD of **8** = 130 mg/kg. However, **5** showed no improvement in a mammalian bioaccumulation study, with **8** being the only observable metabolite. We also failed to observe any improvement in soil degradation with this particular compound.

Other carboalkoxylated pyrazolines such as **9**, **10**, and **11** were also synthesized (Figure 6). In general, these analogs lacked the requisite commercial level efficacy to warrant further environmental and biological fate studies.

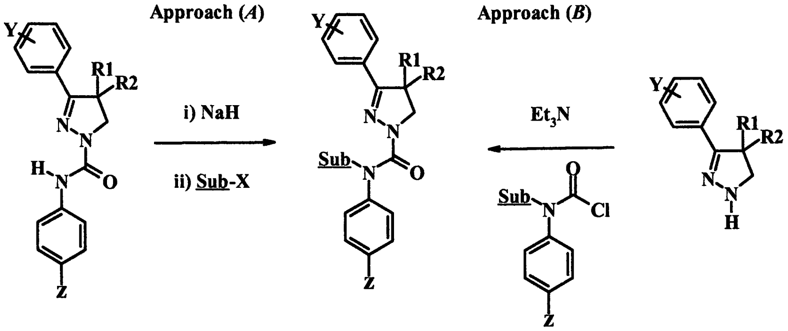
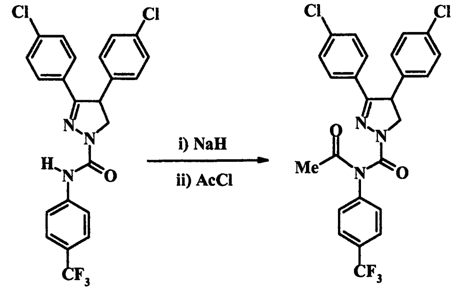

Approach (A)
i) NaH
ii) Sub-X
Approach (B)
Et3N
Y
R1
R2
N
H
O
Z
Sub
Cl

Figure 3. Synthesis of N-substituted pyrazolines.

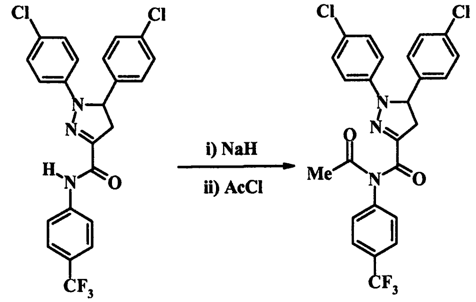

Cl
N
H
O
CF3
i) NaH
ii) AcCl
Me

1

λ_{max} = 310 nm

2

λ_{max} = 290 nm


Cl
N
H
O
CF3
i) NaH
ii) AcCl
Me

3

λ_{max} = 365 nm

4

λ_{max} = 382 nm

Figure 4. Synthesis of N-acetylated pyrazoline analogs.

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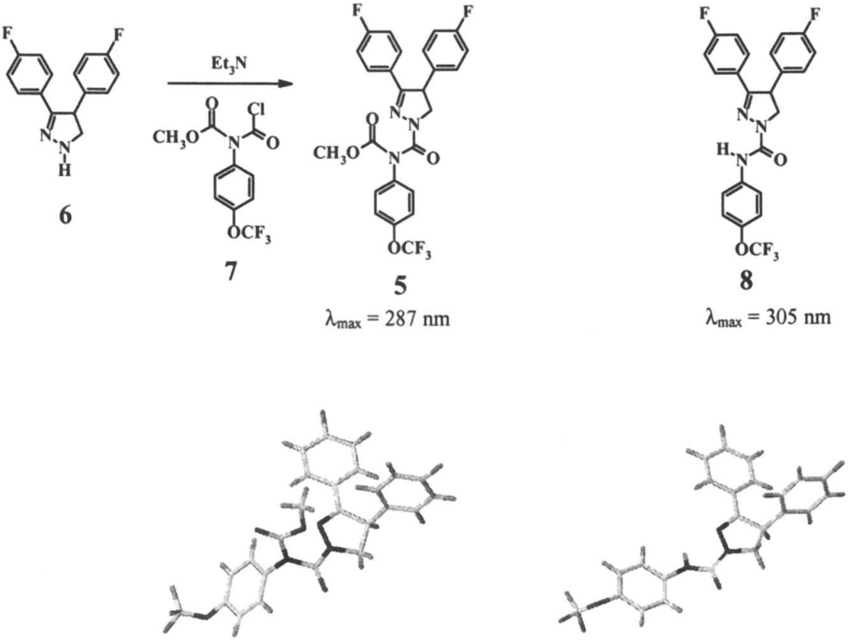
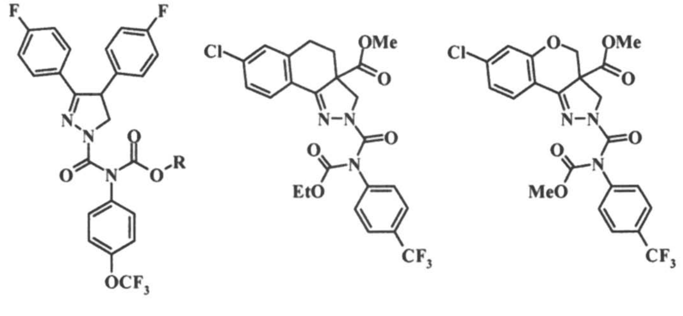


x-ray structure of **5**

x-ray structure of **8**

*Figure 5. Synthesis and structure of N-carbomethoxy pyrazoline **5**.*



9
R = Et, *i*-Pr, *n*-Octyl, *t*-Bu

10

11

Figure 6. N-carboalkoxy pyrazolines.

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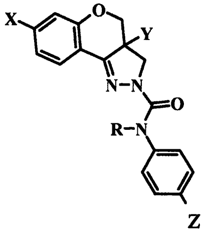
N-Alkyl Oxyindazoles

We have also prepared a series of N-alkyl substituted oxyindazoles **12** as depicted in Figure 7 (*9*). All analogs show reasonably good levels of insecticidal activity which seems to increase with the apparent ease of *in vivo* cleavage of the R group. Thus for the same X, Y, and Z groups, the activity of the compound follows the order of R = Me, CH_2OMe, Et > $CH_2C{\equiv}CH$, Pr > CH_2Ph, CH_2CO_2Me.



12

X = F, Cl, CF_3

Y = *i*Pr, Me, CO_2Me

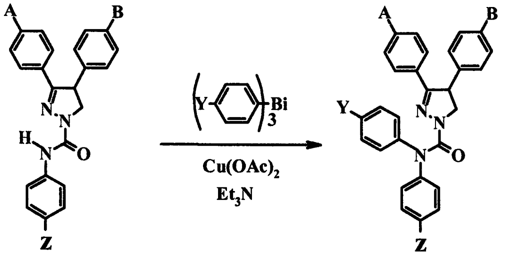
Z = Br, CF_3

R = Me
Et
*n*Pr
CH_2OMe
CH_2CO_2Me
$CH_2CO_2t\text{Bu}$
CH_2Ph
CH_2CN
$CH_2CH{=}CH_2$
$CH_2C{\equiv}CH$

Figure 7. N-alkyl oxyindazoles.

N-Aryl Pyrazolines

An aryl substituent can be introduced onto the nitrogen of the pyrazoline scaffold using the bismuth N-arylation chemistry that we have developed in our laboratory (Figure 8) (*10*). It is interesting to note that most of these N-aryl pyrazolines are also quite active with the phenyl analogs (Y=H) showing efficacy against FAW down to the 2.5 ppm level. This observation does present a challenge to the pro-insecticide theory since complete degradation of a phenyl group *in vivo* is relatively rare in biological systems.



A, B = H, F, Cl

Y = H, F, Br

Z = Br, OCF_3

Figure 8. Synthesis of N-aryl pyrazolines.

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N-Amino Oxyindazoles

Amination of the oxyindazole **13** generated the N-amino analog **14**. Further derivatization produced other N-amino compounds **15** – **17** which all exhibited modest levels of insecticidal activity against FAW and TBW (Figure 9).

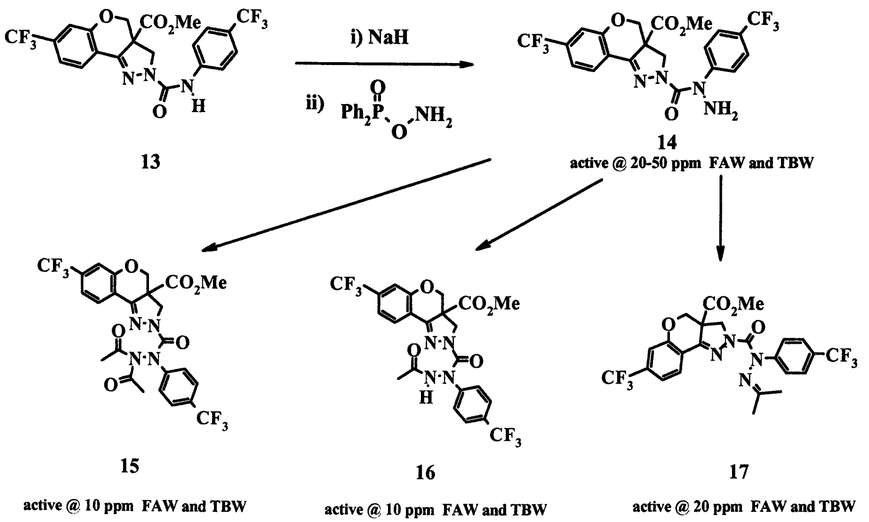
13
i) NaH
ii) Ph2P(O)ONH2
14
active @ 20-50 ppm FAW and TBW
15
active @ 10 ppm FAW and TBW
16
active @ 10 ppm FAW and TBW
17
active @ 20 ppm FAW and TBW

Figure 9. Synthesis of N-amino oxyindazoles.

N-Sulfenyl Pyrazolines

A series of N-sulfenylated pyrazolines were also prepared (Figure 10). These analogs have various levels of efficacy with some even more active than the parent N-H compound, and some with expanded spectrum. It is interesting to note that the size of the R1 group does not seem to affect the activity of these analogs. This observation supports the notion that these sulfenylated pyrazolines are pro-insecticides.

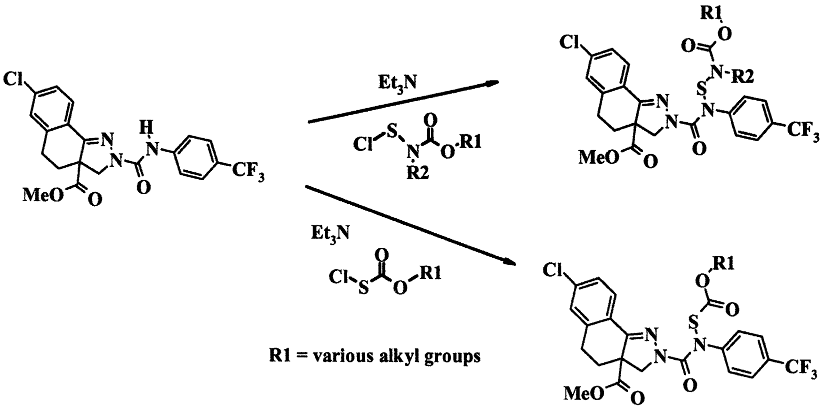

Figure 10. Synthesis of N-sulfenylated pyrazolines.

Intramolecular-assisted Urea Cleavage

The concept of using a tethered nucleophile to assist in the intramolecular cleavage of the urea function as depicted in Figure 11 was also explored. This approach attempts to logically design a system that would realize the pro-insecticide concept described earlier. Thus with a pyrazoline such as **18**, we envisioned that in the soil system the hydroxyethyl linker could help catalyze the hydrolysis of the urea moiety following pathways *a* and/or *b* to generate "innocuous" products **19** – **21**. On the other hand, a dealkylative degradation in the target insects (pathway *c*) would generate the insecticidal metabolite **22** .

Treatment of the precursor **23** under the bismuth arylation conditions for a relatively short time gives mostly starting material and a low yield of the N-arylated product **24**. Interestingly, with prolonged reaction time, along with the O- and bisarylated products **25** and **26**, we indeed observed the formation of the pyrazoline **27** and the cyclic carbamate **28**, and the absence of any N-arylated product **24** (Figure 12). It is tempting to speculate that the latter products are derived from the urea cleavage of **24** which would validate our hypothesis at least in an organic medium.

Indeed the pyrazolines **29** and **30** (Figure 13) do exhibit shortened soil half lives (< 10 days and < 5 days respectively); however, both compounds are only slightly active against FAW and TBW.

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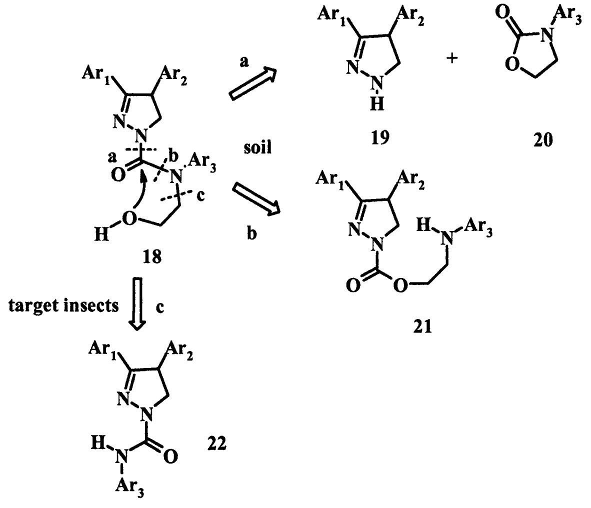
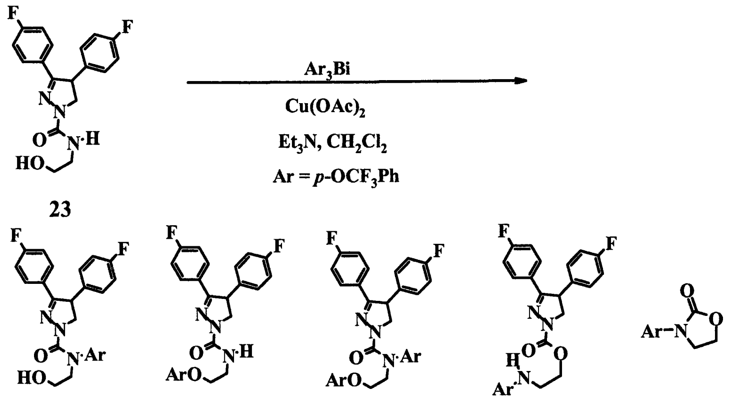

a
soil
b
target insects
c
18
19
20
21
22
+

Figure 11. Intramolecular-assisted urea cleavage.


Ar_3Bi
$Cu(OAc)_2$
Et_3N, CH_2Cl_2
Ar = p-OCF_3Ph
23

	24	25	26	27	28
t = 3h	10%	–	–	–	–
t = 18h	–	36%	10%	24%	7%

Figure 12. Observation of in vitro urea cleavage.

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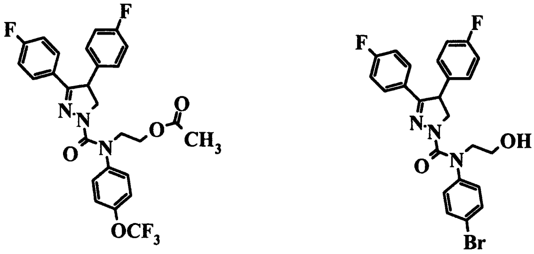

29 30

Figure 13. Tethered pyrazolines.

Conclusions

Novel N-substituted pyrazolines have been synthesized and represent a new class of active insecticides. A number of new routes to these compounds have been developed. In some cases, improved activity and expanded spectrum were observed. Furthermore, soil degradation could be enhanced with specially designed analogs.

Acknowledgements

The authors wish to thank J. Calabrese and W. Marshall of DuPont Central Research for performing x-ray crystal analysis of various pyrazoline analogs. Our thanks also go to G. Lahm for his ideas and support of this project, and S. Riley for performing field trials.

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Chapter 15

Pyridazine Insecticides: Synthesis and Biological Activity

Victor E. Amoo, Charles R. Harrison, George P. Lahm,
Patrick D. Lowder, Thomas M. Stevenson, Jeffrey K. Long,
Rafael Shapiro, Robert W. March, Donald E. Allen,
Mark D. Richmond, Wendy A. March, Gary Chun,
Milagro P. Folgar, and Sandra M. Griswold

Stine-Haskell Research Center, DuPont Agricultural Products, S300, P.O.
Box 30, Newark, DE 19714–0030

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N-arylureas of 3-arylpyridazines have been found to be highly active insecticides. This activity is highly dependent upon the presence of a *meta*-substituent on the 3-aryl ring. In addition, geometrically constrained tricyclic pyridazines have been found to have greater levels of activity. This article will highlight the synthesis and biological activity of these novel insecticides and other closely related ring systems.

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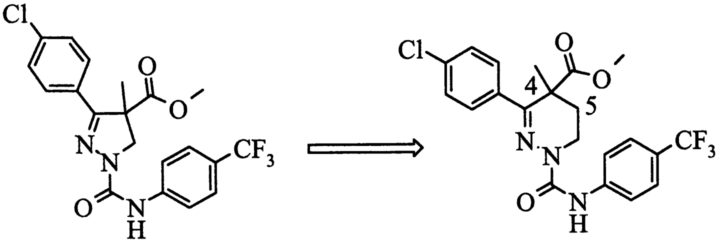


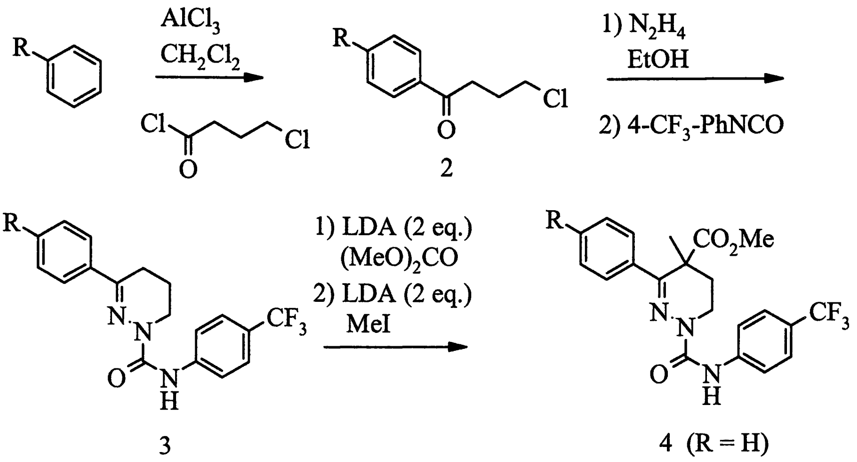
RH 3421

1

Figure 1. Design of Pyridazines

The insecticidal activity of the pyrazoline compounds, exemplified by the Rohm and Haas compound RH3421, has been well-established (1,2). Based on the assumption that the pyridazine ring could act as an isostere of the pyrazoline ring, the synthesis of 1 was investigated (figure 1).

Figure 2 illustrates the synthesis of the unsubstituted and *para*-chloro monocyclic pyridazine analogs **4** and **5** respectively. Friedel-Craft acylation of benzene or chlorobenzene with 4-chlorobutyryl chloride provided the substituted butyrophenone **2**. Cyclization of **2** with hydrazine followed by treatment with 4-trifluoromethylphenyl isocyanate gave the ureas **3**. Double alkylation of the 4-position of **3** via dianions was done stepwise, first using dimethylcarbonate as the electrophile and then with methyl iodide. The unsubstituted analog **4** was moderately active as an insecticide whereas the *para*-chloro analog **5** was inactive. This finding was contradictory to structure-activity relationships of the



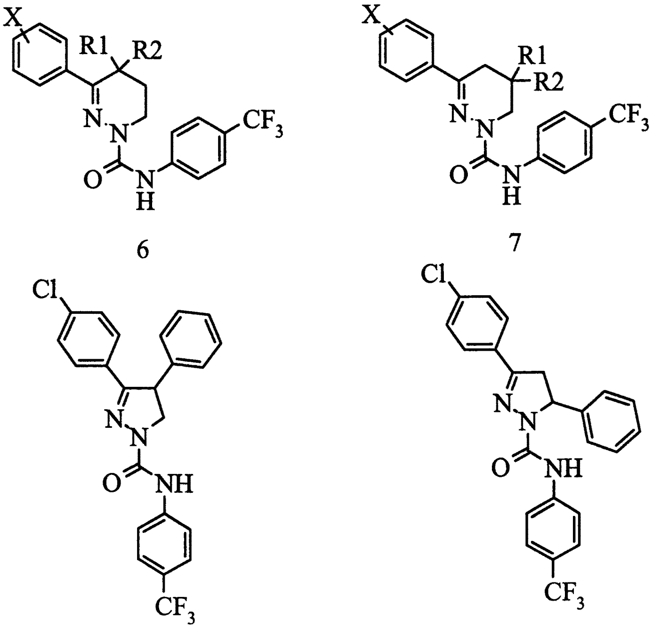
3

4 (R = H)
5 (R = Cl)

Figure2. Synthesis of a Pyridazine Analog of RH3421

analogous pyrazolines where *para*-chloro derivatives are known to be more active than their unsubstituted counterparts.

Because of the lack of activity for compounds like **5**, we wondered if substitution of the pyridazine at the 5-position (as in structure **7**) instead of the 4-position (as in structure **6**) might be more advantageous for activity. This postulation arose from the fact that, in the pyrazoline series both the 3,4 and 3,5-disubstituted analogs **8** and **9** are active insecticides.



6 7 8 9

Figure 3. A Comparison of Pyrazoline and Pyridazine Substitution Patterns

The synthesis of the 3,5-diarylpyridazine **15** was proposed to test the hypothesis. Figure 4 describes two pathways used to synthesize **15**. The 3,5-diphenylpyridazinone **11** was obtained by treatment of the gamma-ketoacid **10** with hydrazine. Reduction of **11** with lithium aluminum hydride afforded the pyridazine **12**, which was coupled with 4-trifluoromethylphenyl isocyanate to give the target compound **15**. Alternatively, a cycloaddition of 1,3-diphenylbutadiene **13** and diethylazodicarboxylate (DEAD) gave the cycloadduct **14** which upon treatment with potassium hydroxide provided the intermediate pyridazine **12**. Compound **15** showed no insecticidal activity indicating that the unexpected structure-activity relationship observed for **4** and **5** could not be attributed to the substitution at the 4-position of the pyridazine ring.

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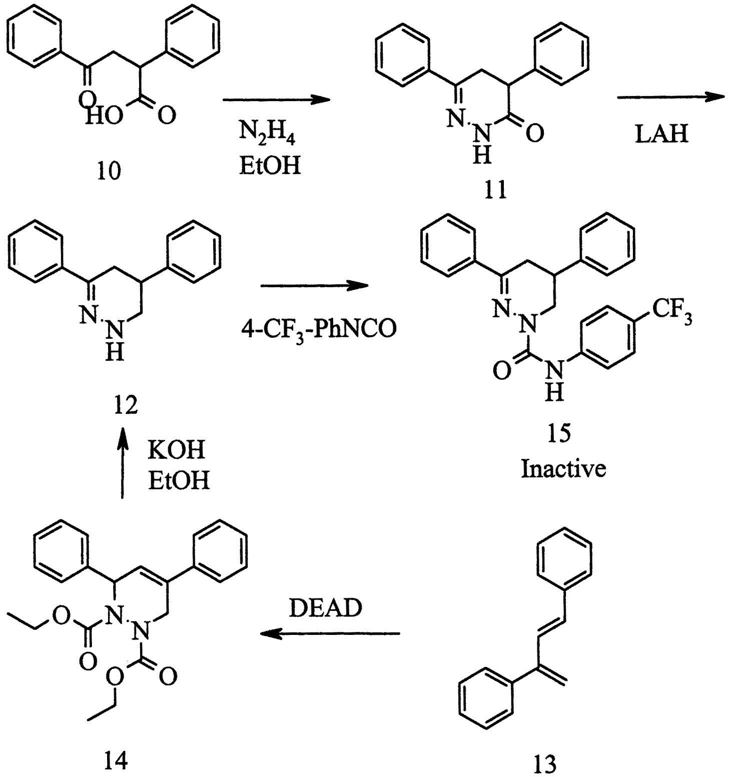

Figure 4. Synthesis of a 3,5-Diarylpyridazine

In light of these results we superimposed molecular models of pyrazolines and pyridazines. This suggested that on the 3-aryl ring the substituent at the *para*-position of a pyrazoline occupied a similar position in space as the *meta*-substituent of a pyridazine ring. Thus the synthesis of 3,4-diarylpyridazines with *meta*-substitution on the 3-aryl ring was investigated. This synthesis began with the alkylation of the substituted deoxybenzoins **16** with ethyl bromoacetate and carried along as previously described (Figure 5). In order to assure ourselves of the importance of the position of substitution on the 3-aryl ring we also explored *ortho*- and *para*-substituents on this ring. As expected from the observed overlap from molecular modeling, the *meta*-substituted 3-phenylpyridazines were shown to be highly active insecticides.

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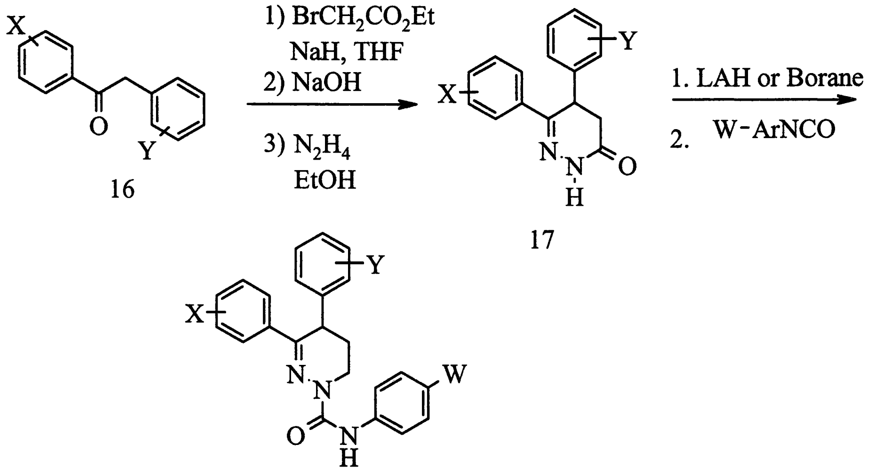
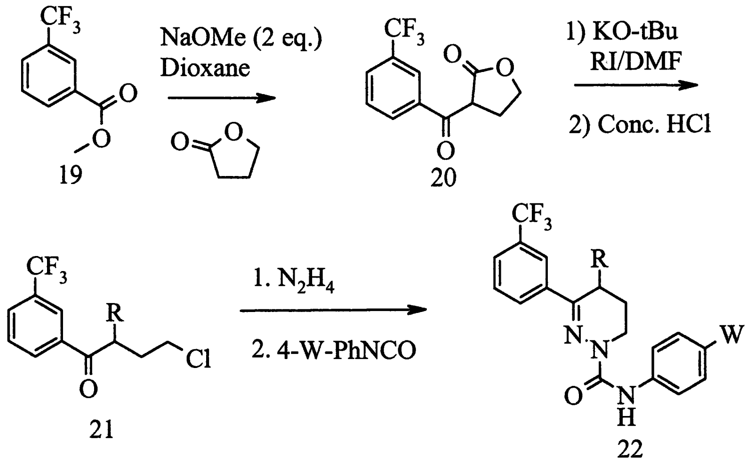

X
O
Y
16
1) $BrCH_2CO_2Et$
NaH, THF
2) NaOH
3) N_2H_4
EtOH
Y
X
N
N
H
O
17
1. LAH or Borane
2. W-ArNCO
Y
X
N
N
O
N
H
W

18

Figure 5. Synthesis of 3,4-Diarylpyridazines

The synthesis of 4-alkyl pyridazines **22** is described in Figure 6. The *meta*-substituted benzoic ester **19** was converted to the keto lactone **20** by reaction with gamma-butyrolactone in the presence of sodium methoxide. Alkylation proceeded smoothly with potassium t-butoxide to introduce the R-substituent. Acidic hydrolysis of the lactone was accompanied by decarboxylation and concomitant chlorination to give the substituted chloro butyrophenone **21**. The target compounds **22** were obtained by cyclization of **21** with hydrazine and coupling with aryl isocyanates.


CF_3
O
O
19
NaOMe (2 eq.)
Dioxane
O
O
CF_3
O
O
O
20
1) KO-tBu
RI/DMF
2) Conc. HCl
CF_3
R
Cl
O
21
1. N_2H_4
2. 4-W-PhNCO
CF_3
R
N
N
O
N
H
W

22

Figure 6. Synthetic Route to 4-Alkylpyridazines

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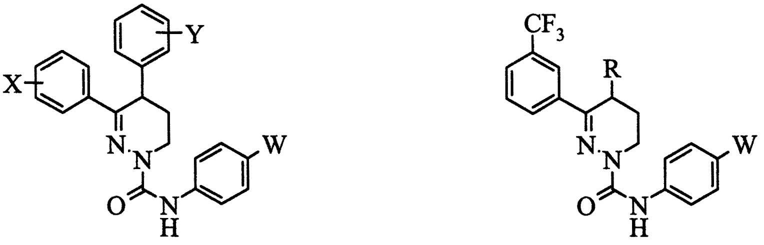
Figure 7 summarizes the structure-activity relationships of the monocyclic pyridazines. On the 3-aryl ring, the X-substituent must be in the *meta*-position for good levels of activity. Structure activity for the Y- and W-substituents followed established trends previously seen for pyrazolines. In the 4-alkyl series **22**, highest activity was seen when R was *n*-butyl. Lepidopteran insects were found to be the most susceptible to the monocyclic pyridazines. A representative compound of structure **18** with X as 3-CF_3, Y as 4-F, and W as 4-OCF_3 had activity on fall armyworm at 2.5 ppm with good residual activity.



18

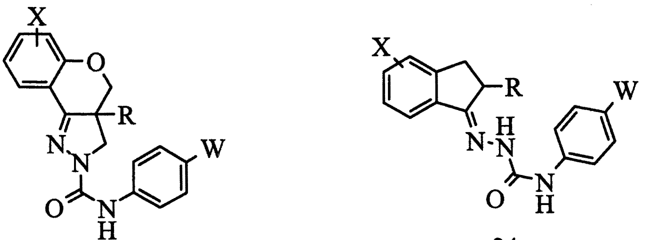
22

X = *m*-substituted >> *p*-substituted
3-CF_3 > 3-Cl > 3-F > H
Y = *p*-substituted >> *m*-substituted
4-F > 4-Cl > 4-CF_3 > H
W = *p*-substituted best
4-CF_3 = 4-OCF_3 > 4-Br > 4-Cl

R = *n*-Bu > *n*-Pr > H

Figure 7. Structure-Activity Relationships for 4-Substituted Pyridazines

Previous research in our laboratories has demonstrated that conformationally restricted analogs of pyrazolines such as **23** (3, 4) and semicarbazones such as **24** (5) retain high insecticidal activity (Figure 8).



23

24

Figure 8. Conformationally Restricted Pyrazoline Analogs

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Prompted by these observations, the synthesis of the conformationally restrained pyridazine analogs **26** and **27** was undertaken (Figure 9). Previous experience with compounds such as **23** showed that 6-membered ring fused compounds had highest levels of activity. Conversely, semicarbazones such as **24** showed highest activity when derived from 5-membered ring fusion. Again, comparison of molecular models of both **23** and **24** with **26** and **27** was informative. These comparisons predicted that compounds of structure **27** would have the best overlap.

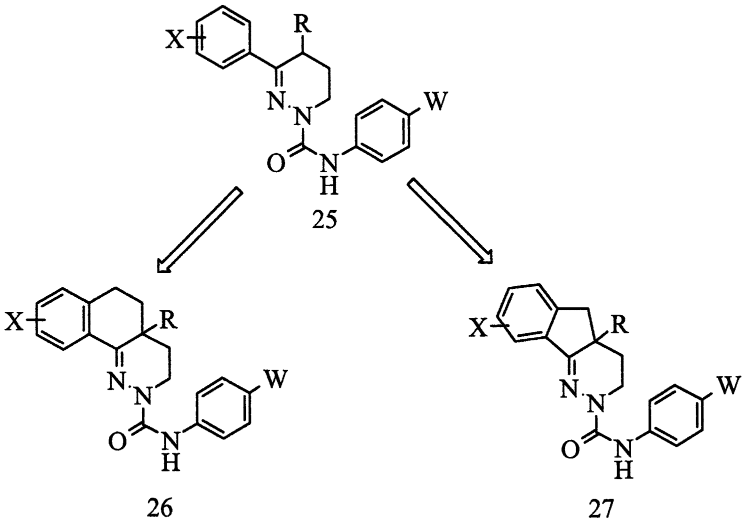

Figure 9. Conformationally Restricted Pyridazines

The angular alkyl and phenyl compounds of structure **27** where R is alkyl or substituted phenyl) were synthesized as shown in Figure 10. The route was based on the chemistry previously described in Figure 5 for monocyclic pyridazines. Starting with indanones **28** the tricyclic skeleton was constructed by alkylation with ethyl bromoacetate, ester hydrolysis and cyclization with hydrazine to give pyridazinone **29**. Selective reduction of the amide in the presence of the hydrazone function was achieved with both diborane and lithium aluminum hydride. The pyridazines were then converted in high yield to the final products **27** with aryl isocyanates. This route allowed synthesis of tricyclic pyridazines with a wide variety of aryl and alkyl R-substituents. As predicted, compounds of structure **27** had high insecticidal activity while analogs of structure **26** (made from tetralones in an analogous manner to **27**) had significantly less activity.

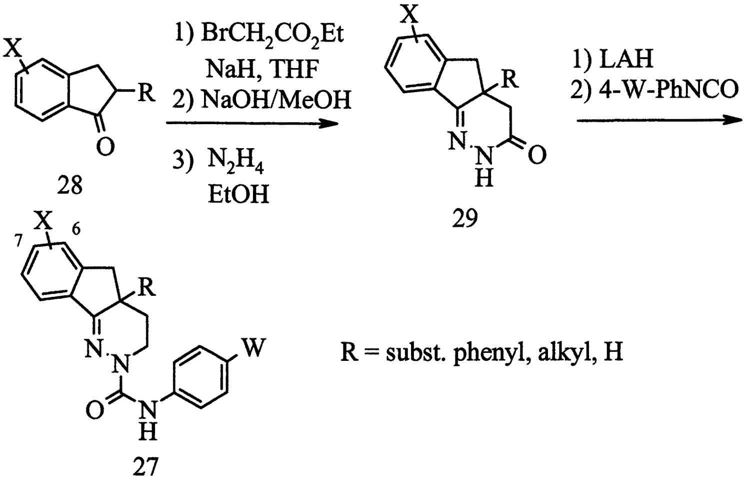
X
R
O
28
1) $BrCH_2CO_2Et$
NaH, THF
2) NaOH/MeOH
3) N_2H_4
EtOH
X
R
N
N
H
O
29
1) LAH
2) 4-W-PhNCO
X
7
6
R
N
N
W
O
N
H
27
R = subst. phenyl, alkyl, H

Figure 10. Synthesis of Tricyclic Pyridazines

The angular carbomethoxy analogs such as **30** were synthesized via a slightly modified route as exemplified in Figure 11. Since the carbomethoxy group could not withstand the amide reduction conditions, the 2-carbons of the pyridazine were introduced with dibromoethane rather than ethyl bromoacetate. This route was effective for small scale synthesis of **30**, but proved difficult to scale up.

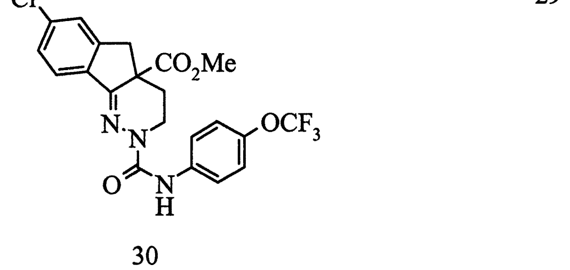
Cl
CO_2Me
O
28
1) $BrCH_2CH_2Br$
NaH/DMF
2) N_2H_4
EtOH
Cl
CO_2Me
N
N
H
29
4-OCF_3-PhNCO
Cl
CO_2Me
N
N
OCF_3
O
N
H
30

Figure 11. Synthesis of Angular Carbomethoxy Tricyclic Pyridazines

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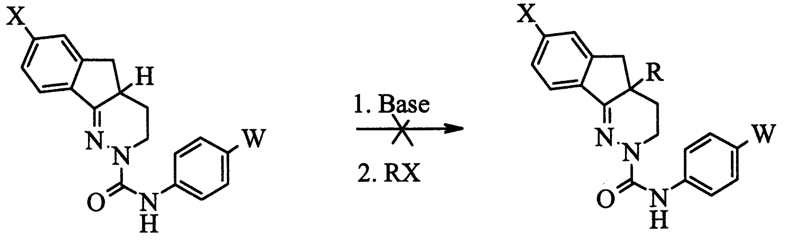
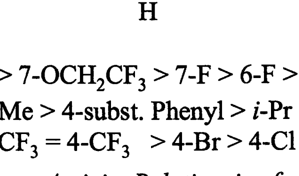
A more efficient, convergent method for synthesizing the angular alkyl and carbomethoxy analogs of the tricyclic pyridazines would involve alkylation or acylation of a dianion of the intermediate **31**. However, as shown in Figure 12, attempts to effect alkylation or acylation of **31** at the ring junction using different bases and electrophiles proved unsuccessful.



31 32

Figure 12. Attempted Introduction of Angular Substituents by Dianion Chemistry

The structure-activity relationships of tricyclic pyridazines **27** is summarized in Figure 13. The relationships for substituents X, R and W generally followed known trends. The tricyclic pyridazines were more active than the corresponding monocyclic pyridazines **18** (Figure 7). Substitution at the 7-position produced more active compounds than those substituted at the 6-position. At the angular position, carbomethoxy derivatives were the most active insecticides.



X = 7-Cl > 7-OCH_2CF_3 > 7-F > 6-F > 6-Cl > H
R = COOMe > 4-subst. Phenyl > *i*-Pr > Et > Me > H
W = 4-OCF_3 = 4-CF_3 > 4-Br > 4-Cl

Figure 13. Structure Activity Relationsips for Tricyclic Pyridazines

The pyridazine insecticides showed excellent activity against a broad spectrum of lepidopteran pests. Compound **30** (Figure 11) showed especially interesting activity with LD_{80}'s of 0.2 ppm for fall armyworm, and 0.5 ppm for tobacco budworm. Compound **30** was chosen for field evaluation based on the excellent greenhouse results. In field trials on vegetables and cotton against fall armyworm, cabbage looper, diamondback moth and tobacco budworm **30** had activity at rates as low as 10-20 g/ha. Unfortunately, **30** was degraded slowly in soil and proved difficult to prepare on large scale. Therefore commercialization of this class was not pursued, but subsequent research based on 6-membered ring compounds ultimately produced the commercial insecticide Indoxacarb.

Conclusions

In conclusion, pyridazine insecticides are highly active compounds with efficacy similar to pyrazolines. For monocyclic pyridazines, structure-activity relationships deviate from pyrazolines by showing a preference for *meta*-substitution on the 3-aryl ring. Other aspects of structure activity are similar to pyrazolines. The tricyclic pyridazines especially with angular carbomethoxy groups show excellent levels of insecticidal activity. These compounds proved that the 5-membered ring found in the original pyrazolines was not sacrosanct. Compounds such as **30** served as the structural template for the discovery of the oxadiazine insecticides (6) and ultimately the new commercial lepidopteran insecticide Indoxacarb.

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Chapter 16

Synthesis and Biological Activity of Oxadiazine and Triazine Insecticides: The Discovery of Indoxacarb

Stephen F. McCann, Gary D. Annis, Rafael Shapiro,
David W. Piotrowski, George P. Lahm, Jeffrey K. Long,
Kevin C. Lee, Margaret M. Hughes, Brian J. Myers,
Sandra M. Griswold, Bonita M. Reeves, Robert W. March,
Paula L. Sharpe, Patrick Lowder, Paul Tseng, William E. Barnette,
and Keith D. Wing

Stine-Haskell Research Center, DuPont Agricultural Products, P.O. Box 30, Newark, DE 19714–0030

Indoxacarb (Steward^{TM}, Avaunt^{TM}) was discovered as a result of extensive analoging around the pyrazoline-based sodium channel blocking insecticides. Indoxacarb is an oxadiazine, which evolved from the pyrazoline moiety via the analogous pyridazines. Compared to the pyridazines, oxadiazines typically showed improved soil degradation rates, were easier to synthesize, and had equally-high levels of insecticidal efficacy. Analoging in the oxadiazines led to the identification of the racemic form of indoxacarb (DPX-JW062) as a commercial candidate. Chiral synthesis identified the S-enantiomer (indoxacarb) as the active product.

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

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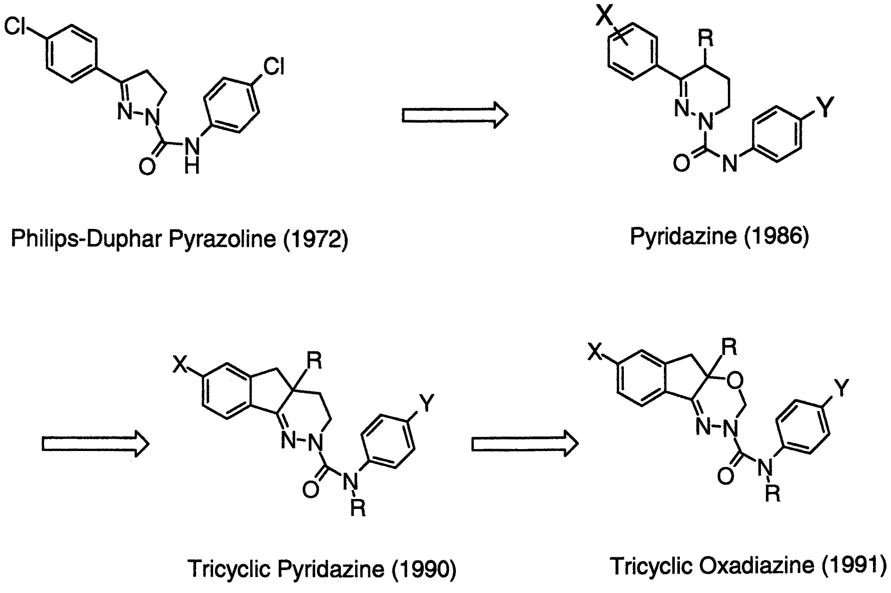
INTRODUCTION

The discovery of crop insecticides having novel modes-of-action is vital towards managing pest strains that are resistant to existing compounds. The pyrazoline insecticides, originally discovered by Philips-Duphar *(1)* in 1972, are a class of highly active insecticides with a novel mode-of-action, namely, the blocking of sodium channels *(2)*. Previous chapters in this book have described the "evolution" of the pyrazoline-type insecticides. Various structural subclasses which mimic the toxiphore of the original Philips-Duphar pyrazoline *(3)* were described, including semicarbazones *(4)* , pyrazoline carboxanilides *(5)*, pyridazines *(6)*, as well as conformationally-constrained, fused-tricyclic pyrazolines (indazoles and oxyindazoles) *(7)* and pyridazines *(6)*. It was shown that similar angular-group topologies for the subclasses accounted for similar interclass structure-activity trends *(8)*.

The oxadiazine subclass of sodium channel blocking insecticides was a derivation of the tricyclic pyridazine compounds wherein the pyridazine-ring C-5 methylene is replaced with an oxygen atom (Figure 1).



Philips-Duphar Pyrazoline (1972)

Pyridazine (1986)

Tricyclic Pyridazine (1990)

Tricyclic Oxadiazine (1991)

Figure 1. Pyrazoline "evolution" leading to oxadiazines

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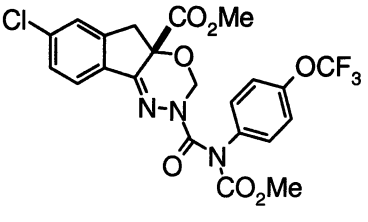
It was envisioned that the introduction of a heteroatom into the pyridazine ring would lead to compounds that: 1) degrade more quickly in the soil; 2) are easier to synthesize, and; 3) maintain the high insecticidal efficacies shown by pyridazines due to structural similarity. It turns out that all three of these attributes were observed for the oxadiazines. Applying the extensive pyrazoline/pyridazine structure-activity knowledge to the preparation of oxadiazines, the commercialization candidate DPX-JW062 (racemic indoxacarb) was rapidly identified. Subsequent development of an asymmetric synthesis of this chiral molecule resulted in the preparation of indoxacarb in 50% enantiomeric excess (DPX-MP062, Figure 2) which is sold commercially as a 75:25 mixture of active (S) and inactive (R) enantiomers . The following chapter outlines the chemistry and biological activity of the oxadiazine analogs leading to the discovery of indoxacarb.



Indoxacarb

Figure 2. Structure of indoxacarb (DPX-MP062, Steward ®, Avaunt ®)

Oxadiazine Synthesis

Retrosythetic analysis of the tricyclic oxadiazine target structures revealed three key steps in their syntheses: 1) oxidative hydroxylation of an indanone precursor, 2) formation of a semicarbazone, and, 3) ring closure of the hydroxy-semicarbazone via formation of an O, N- acetal of formaldehyde (Figure 3). In the first step, we found that indanone hydroxylations could be achieved under a variety of conditions, usually dictated by the nature of the 2-substituent of the starting indanone (Figure 4). In the cases of indanones substituted with 2-ester

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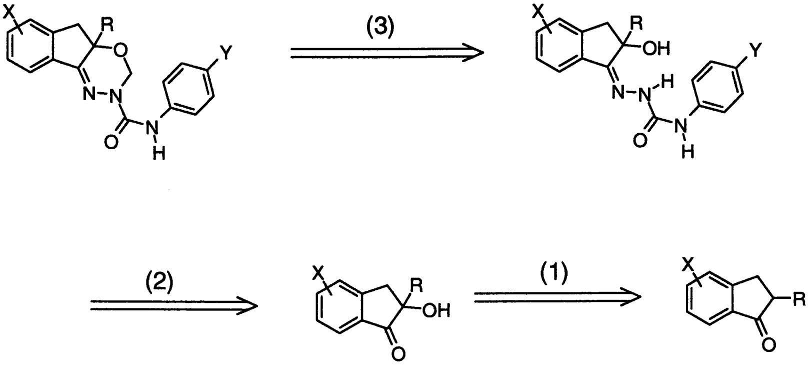
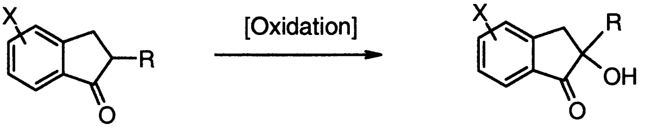


Figure 3. Retrosynthetic analysis of tricyclic oxadiazines



R	*Preferred Reaction Conditions*
Esters	Peracids, H_2O_2 + $NaHCO_3$, Oxone ®, air, etc.
Aryls	Oxone ® + NaOH, air + NaOH + $P(O)(OEt)_3$
Alkyls	TMS-triflate + pyridine, followed by MCPBA (Rubottom procedure)

Figure 4. Indanone hydroxylation procedures.

substituents, a variety of mild oxidation conditions were found to be effective, including MPCBA *(9, 15)*, hydrogen peroxide/ sodium bicarbonate *(10)*, and, in some cases, air. When the 2-substituent was an aryl group, the use of more basic conditions were typically necessary, using, e.g., oxone ® and NaOH or air with NaOH under phase transfer conditions *(11, 15)*. With 2-alkyl substituted indanones, the above procedures were low-yielding, or, in the case of bulky alkyl groups (like i-Pr), no reaction occurred. In these cases, the two-step Rubottom procedure *(12)* proved to be most effacacious (formation of the TMS-enol ether using TMS-triflate followed by oxidation with MCPBA). Similar procedures were used to hydroxylate tetralones and quinolinones.

In the next step, formation of the semicarbazone intermediate, one of two complimentary procedures can be used depending upon the substituent on the aniline nitrogen (Figure 5).

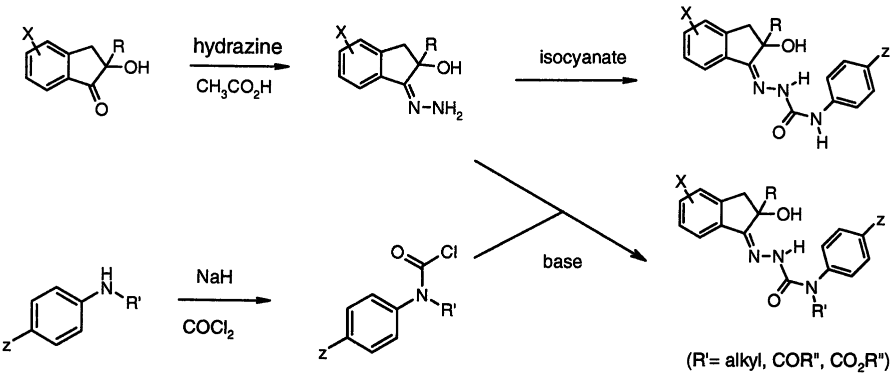


Figure 5. Semicarbazone formation.

One procedure involved initial formation of the hydrazone followed by reaction with a phenyl isocyanate to give the semicarbazone precursors to the tricyclic oxadiazines *(13, 15)*. In cases where the desired oxadiazine product contained a substituent on the carboxanilide nitrogen, an alternative semicarbazone synthesis procedure involving reaction of the hydrazone intermediate with a tertiary carbamoyl chloride was a preferred synthesis option *(14)*. Both approaches gave high yields of the desired semicarbazone products.

Cyclization of the 2-hydroxy semicarbazones to give the target oxadiazines was accomplished using either paraformaldehyde and catalytic TsOH in refluxing acetonitrile *(15)* (for products with a free aniline NH) or with methylal/P_2O_5 *(14)* (for products with substitution on the aniline nitrogen, Figure 6). Substitution at the aniline nitrogen could also be installed by treating the NH-oxadiazine with an alkylating or acylating agent (acid chlorides, acid anhydrides, and chloroformates) in the presence of a hydride base *(15)*.
Analogous triazines could be prepared similarly *(15) (Figure 7)*. The first step involved amination of the indanone using cyclohexyl spiro-oxaziridine *(16)*. Reaction with an aryl semicarbazide under acid catalysis gave 2-amino

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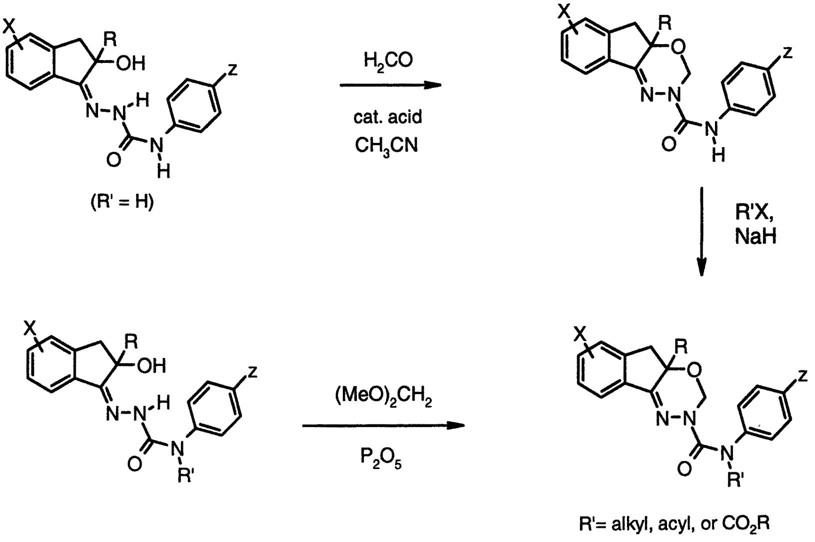

X
R
OH
N-N
H
O
N
H
Z
(R' = H)
H_2CO
cat. acid
CH_3CN
X
R
O
N-N
O
N
H
Z
R'X,
NaH
X
R
OH
N-N
H
O
N
R'
Z
$(MeO)_2CH_2$
P_2O_5
X
R
O
N-N
O
N
R'
Z
R'= alkyl, acyl, or CO_2R

Figure 6. Oxadiazine-ring synthesis via O, N-acetal formation

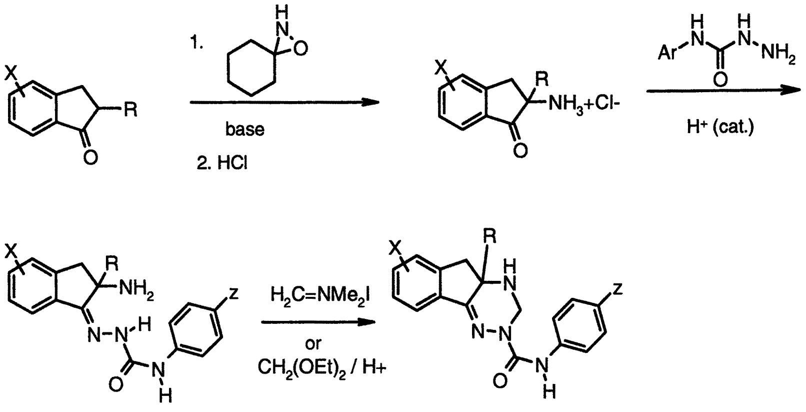
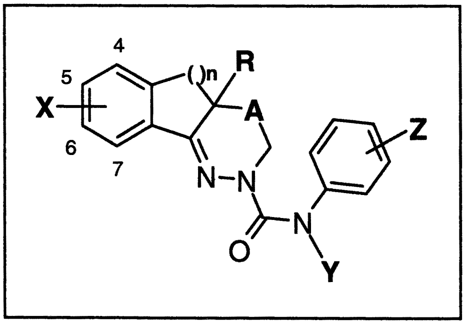

X
R
O
1.
H
N
O
base
2. HCl
X
R
NH_3+Cl-
O
Ar
H
N
H
N
NH_2
O
H+ (cat.)
X
R
NH_2
N-N
H
O
N
H
Z
$H_2C{=}NMe_2I$
or
$CH_2(OEt)_2$ / H+
X
R
H
N
N-N
O
N
H
Z

Figure 7. Synthesis of tricyclic triazines

semicarbazones which undergo cyclization to tricyclic triazines using ethylal and acid catalysis or Eschenmoser's salt. Further structural modifications were possible via the functionalization of either the triazine and/or the carboxanilide nitrogen atoms.

Structure-Activity Relationships (S.A.R.)

The S.A.R. for oxadiazines vs. fall armyworm (*Spodoptera frugiperda*) is summarized in Figure 8. X-Substituents at the 4- or 5- positions of the benzo-ring gave analogs with the highest activity, and, of those substituents, Cl, Br, CF_3 and OCH_2CF_3 were best. The angular R-group was either 4-halophenyl or carbomethoxy in the most active analogs, with alkyl substituents and higher esters giving lower levels of activity. The Z-substituent on the phenyl ring of the carboxanilide was typically para for the most active analogs, and the Z-substituent was usually OCF_3 or CF_3. Carbomethoxy or acetyl for Y gave the best activity for derivatives substituted at the carboxanilide nitrogen.



A = O, NR' are comparable in activity

n = 1 > 2

R = 4-F-Ph, CO_2Me > Ph, CO_2Et, Et
> 4-Cl-Ph, Me, i-Pr, CO_2i-Pr

X= Cl, Br, OCH_2CF_3, CF_3
> F, OCF3 > H, alkyl

4 or 5 substitution better
than 6 or 7 substitution (n=1)
4 better than 5, 6, or 7 (n=2)

Y = CO_2Me, $COCH_3$ > H, Me, Et,
CO_2Et, allyl, propargyl, n-Pr,
COEt, CO(i-Pr) > CH_2CO_2Me, Bn
>higher alkyl

Z = OCF_3 > CF_3 > Br, $OCHF_2$
> Cl > F > OMe, NO_2, alkyl
para > meta

Figure 8. S.A.R. for oxadiazines vs. Spodoptera frugiperda (note: substituents giving highest activities are listed first and relative activities are listed in descending order).

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Oxadiazines and triazines with the same substitution patterns (i.e. same R, X, and Z substituents) tended to be comparable in activity. Tetralone-derived oxadiazines (n = 2) were slightly less active than the indanone-derived counterparts (n = 1). The S.A.R. for tetralone-derived oxadiazines (n = 2) was similar to the indanone-derived compounds except that the benzo-ring X-substituent needed to be in the "4-position" for highest activity (using Figure 8 numbering system).

Commercialization Candidate DPX-JW062

Based on overall considerations of insecticidal efficacy (vs. multiple species of *spodoptera, heliothis, plutella, trichoplusia and cydia*), safety to non-target organisms (e.g. predatory insects, birds, fish), favorable mammalian toxicicity, and rapid dissipation in soil and in aqueous systems, the compound DPX-JW062 was selected for advanced pre-commercialization studies *(Fig. 9)*. DPX-JW062 was also found to be highly active towards insect strains that had developed resistance towards the use of organophosphates, carbamates and pyrethroids *(17)*. DPX-JW062 was found to be active via blocking of the sodium channel in insects, the same mode-of-action as previously reported for insecticidal pyrazolines *(18, 19)*.

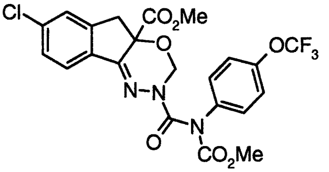

Figure 9. Commercialization candidate DPX-JW062 (racemic indoxacarb).

DPX-JW062 is a racemic molecule. Since the identity of the angular substituent at the chiral center of oxadiazines and other pyrazoline-type compounds was important in determining insecticidal activity, and since it had been previously shown that chiral pyrazolines have an active and an inactive enantiomer *(20)*, we sought to prepare the individual enantiomers of DPX-JW062. The racemic mixture was separated by chiral HPLC and the resulting enantiomers were tested for insecticidal activity *(Figure 10)*. Indeed, the (+)-enantiomer, DPX-KN128 [(+)-DPX-JW062] was found to be twice as active as the racemic DPX-JW062, while the (-)-enantiomer was completely inactive. Thus, a chiral synthesis of (+)-DPX-JW062 was an important goal.

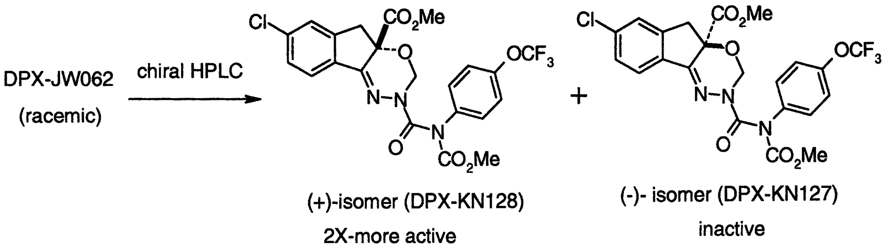
DPX-JW062
(racemic)
chiral HPLC
Cl
CO_2Me
O
OCF_3
N-N
O
N
CO_2Me
+
(+)-isomer (DPX-KN128)
2X-more active
(-)- isomer (DPX-KN127)
inactive

Figure 10. Separation of DPX-JW062 enantiomers

In the synthesis of DPX-JW062, introduction of chirality occurs in the hydroxylation of the 2-carbomethoxy indanone *(Fig. 11)*. An asymmetric approach to this oxidation was therefore sought.

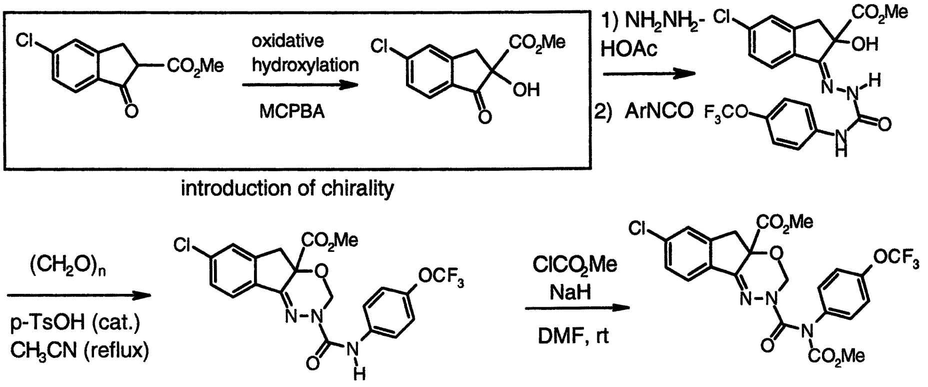
Cl
CO_2Me
O
oxidative
hydroxylation
MCPBA
OH
introduction of chirality
1) NH_2NH_2- HOAc
2) ArNCO
N-N-H
F_3CO
N
H
O
$(CH_2O)_n$
p-TsOH (cat.)
CH_3CN (reflux)
OCF_3
$ClCO_2Me$
NaH
DMF, rt

Figure 11. Synthesis of racemic DPX-JW062. The first step in this synthesis introduces the chiral center found in the final product.

We investigated a number of procedures for asymmetric synthesis of the hydroxy-indanone intermediate. We found that the use of the Sharpless asymmetric di-hydroxylation reagent (AD-mix, *21*) effected the asymmetric hydroxylation of the carbomethoxy indanone *(Figure 12)*. The AD-mix α and AD-mix β reagents gave 54% and 51% e.e., respectively, of the (+)-(S)- and (-)-(R)- isomers *(29)* of the chiral hydroxy-indanone intermediates which could each be purified to >90% e.e. by recrystallization from ethyl acetate and then carried through the synthesis scheme shown in Figure 11 to obtain pure DPX-JW062

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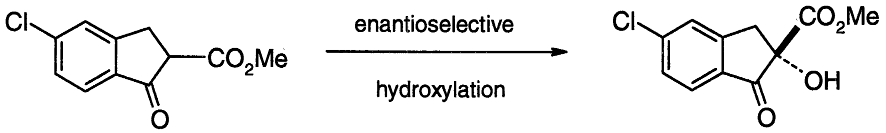
enantiomers. The use of Davis' chiral camphorsulfonyl-oxaziridine reagents *(22)* gave 20-30% e.e. of the hydroxy indanone (best for the "unsubstituted" camphor reagents) while other oxidation procedures (e.g. Sharpless *(23)* and Jacobsen *(24)* asymmetric epoxidation procedures) failed to deliver enantiomerically-enriched hydroxy indanone. Another approach involving use of t-butyl hydroperoxide as the oxidant and cinchonine as a chiral base was later developed which led to formation of the (+)-(S)-hydroxy indanone in 50% e.e. and in high yields *(27, 28)*. Details of this practical modification can be found in the subsequent chapter in this book *(28)*. The current manufacture of indoxacarb involves the use of 50% e.e. (+)-(S)-indanone to prepare 50% e.e. (+)-(S)-indoxacarb (i.e. DPX-MP062).



Procedure	*Conditions*	*%Yield*	*%e.e.*
Sharpless AD-mix-β[21,25]	0°C -> r.t.	30	50 (+-isomer)
Davis oxaziridine[22,26]	0°C, $NaHCO_3$	85	25-30 (+)
Jacobsen Mn-salen oxidation[24]	Various	0-100	0
Sharpless epoxidation [23]	Various	0	0

Figure 12. Selected asymmetric hydroxylation reactions towards the preparation of the (+)(S)-hydroxy indanone isomer.

Conclusions

Indoxacarb represents the first commercialized insecticide that acts by blocking the sodium channel in neurons, a mode-of-action first identified in pyrazolines. The discovery of indoxacarb was achieved by an extensive effort towards optimizing the pyrazoline-type chemistry with regards to insecticidal efficacy, safety towards non-target organisms, and safety towards the environment. Variations to the pyrazoline nucleus led to the finding that structurally-related oxadiazines were also highly insecticidal. Optimization of the oxadiazines led to the identification of racemic indoxacarb (DPX-JW062) as a candidate for commercialization. Chiral synthesis provided a means of producing the enantiomerically-enriched active isomer, indoxacarb.

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Chapter 17

Toward the Manufacture of Indoxacarb

R. Shapiro, G. D. Annis, C. T. Blaisdell, D. J. Dumas, J. Fuchs, S. M. Griswold, G. W. Higley, Jr., W. C. Hollinsed, J. J. Mrowca, J. A. Sternberg, and P. Wojtkowski

Agricultural Products Department, Process Development Group, Stine-Haskell Research Center, DuPont, Newark, DE 19714

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The discovery and development of a novel process to the title compound is described. The key step involves an unprecedented enantioselective hydroxylation of the intermediate 2-carboalkoxy-1-indanone **(10)** catalyzed by a cinchona alkaloid. Significant modifications of the original synthesis of the racemic compound were required in order to manufacture the non-racemic product.

Process development for indoxacarb began with efforts directed towards the racemic compound of Scheme 1. This work was undertaken with the view that the methods used in discovery for preparing nonracemic material were not practical for manufacturing purposes. Therefore, the initial target for development was the racemic product and refinement of the synthesis described in the previous chapter was begun (*1*).

Before development of the racemic insecticide could be undertaken in earnest, however, we were required to make a major modification in the final sequence of steps in order to overcome the troublesome final carbomethoxylation step, which could not be forced to complete conversion. Thus, rearranging the original steps, hydrazone **1** was coupled with carbamoyl chloride **2** and the product was cyclized using diethoxymethane (ethylal) or dimethoxymethane (methylal) in the presence of phosphorus pentoxide adsorbed on Celite or sulfur trioxide. Solvent-exchange and crystallization of the crude racemic indoxacarb from methanol removed noxious formaldehyde-derived dark impurities generated in this final step and provided the final product in a high state of purity.

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

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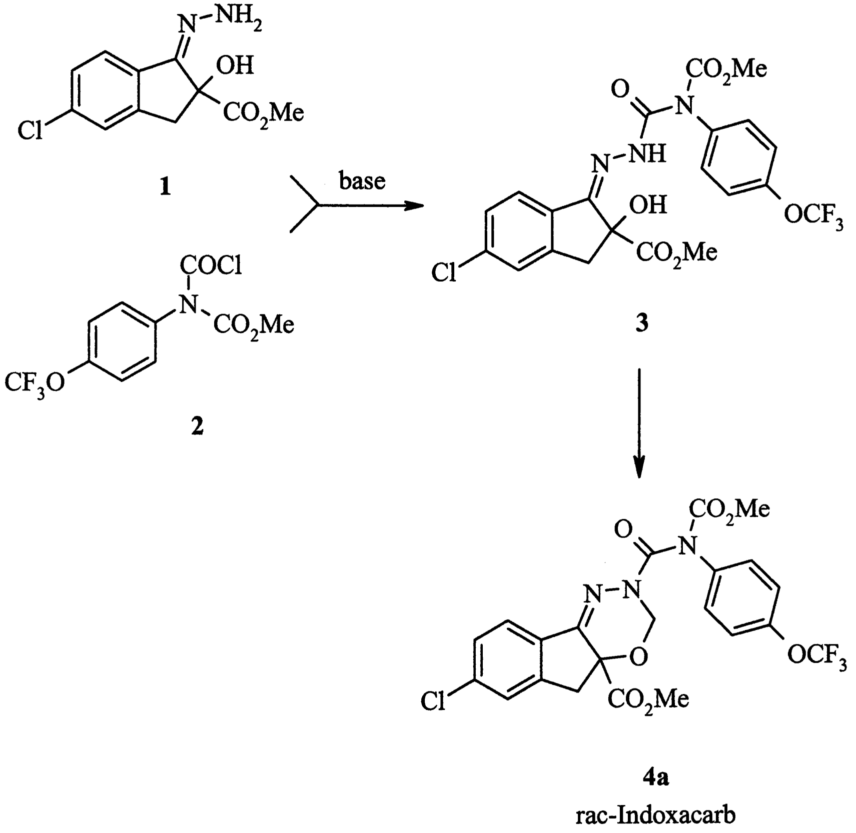
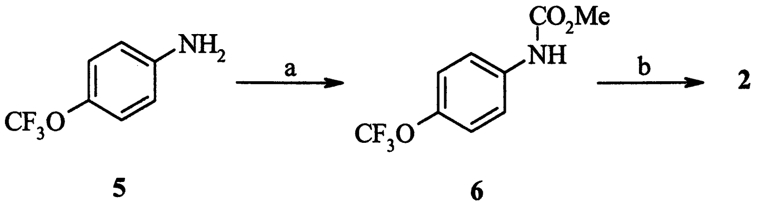


Scheme 1. Synthesis of racemic-Indoxacarb

It should be noted that the cyclocondensation with N-carbomethoxylated semicarbazone **3** was much more difficult than with the non-acylated semicarbazone used in the Discovery synthesis, since the former is much more susceptible to hydrazone cleavage using the typical conditions of paraformaldehyde in the presence of an acid catalyst. Once the phosphorous pentoxide/ethylal/Celite method was discovered, however, process development became a relatively straightforward undertaking. The synthesis of **2** from 4-(trifluoromethoxy)aniline **5** (available by custom-synthesis from anisole in four steps) involves condensation of the sodium salt of its methyl carabamate **6** with excess phosgene. We were able to substitute sodium methoxide in step b for the original more hazardous reagent, sodium hydride (Scheme 2).



Scheme 2. a) MeOCOCl b) NaOMe/PhMe; 3 eqCOCl$_2$

The synthesis of **1** started from commercially-available *m*-chlorobenzaldehyde, **7** (Scheme 3). Malonic acid condensation, followed by hydrogenation, gave the corresponding hydrocinnamic acid **8** in excellent yield, with only traces of dechlorinated product. Standard Friedel-Crafts cyclization of the corresponding acid chloride afforded predominantly the desired indanone regioisomer **9**. Originally, this was carbomethoxylated with dimethyl carbonate in the presence of sodium hydride by analogy with literature conditions. Eventually, we were able to replace sodium hydride with the safer and cheaper sodium methoxide by using careful process control *(2)*. While Oxone had been used previously to oxidize **10** to **11**, we found that inexpensive hydrogen peroxide, in a base-catalyzed procedure, was a superior method for the hydroxylation of **10**, since Baeyer-Villiger side reactions were effectively suppressed. The use of aqueous acetone as a solvent system appeared to minimize ring-opening hydrolysis under the basic conditions by causing the product to precipitate as it was formed. Hydrazone formation with hydrazine acetate, used in excess to suppress formation of the highly insoluble azine byproduct, provided **1** as a mixture of E- and Z-isomers which was not purified, but used directly in the coupling with **2**.

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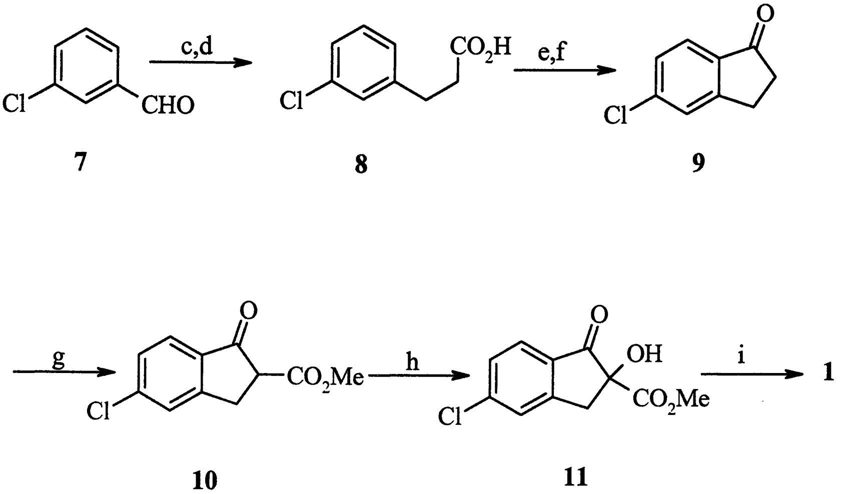

Scheme 3. c) malonic acid d) H_2/Pd-C e) $SOCl_2$ f) $AlCl_3$ g) NaOMe/Me_2CO_3 h) H_2O_2/aq $NaHCO_3$/acetone i) 3 eq NH_2NH_2-HOAc

An alternative, regiospecific route to **10** was investigated, involving the cyclization of p-chlorophenylacetyl chloride with ethylene to form tetralone **13**, followed by oxidative cleavage with buffered peracetic acid and esterification to diester **14** (Scheme 4). One of the advantages of this route was that the Dieckmann cyclization of **14** was easier and cheaper than the sodium hydride mediated carbomethoxylation of **9**. However, after developing this route and comparing costs and hazards we decided not to switch from the *m*-chlorobenzaldehyde process.

Returning to the *m*-chlorobenzaldehyde process, it was during the development of steps g and h that a new asymmetric hydroxylation method was discovered. In order to concatenate the carbomethoxylation step (g) and hydroxylation step (h), we sought to avoid a difficult solvent exchange (toluene to acetone) and effect the hydroxylation of **10** in toluene using an amine base instead of sodium bicarbonate. The triethylammmonium salt of **10** proved to be much more soluble in toluene than the sodium salt, and so the solvent exchange could be eliminated. Furthermore, the discovery that an amine could be used as a hydroxylation catalyst led us to wonder whether a *chiral* amine might also induce enantioselectivity in the process. As luck would have it, one of the first chiral amines tested, cinchonine, gave an enantioselectivity of approximately 3 to 1 (50% e.e.) in the desired sense (enrichment of (S)-enantiomer **11**) (Scheme 5).

Extensive screening of other commercially-available chiral amines provided no improvement over this result, so the development of cinchonine as a catalyst for this reaction was pursued. Derivitization of the OH-group of the catalyst

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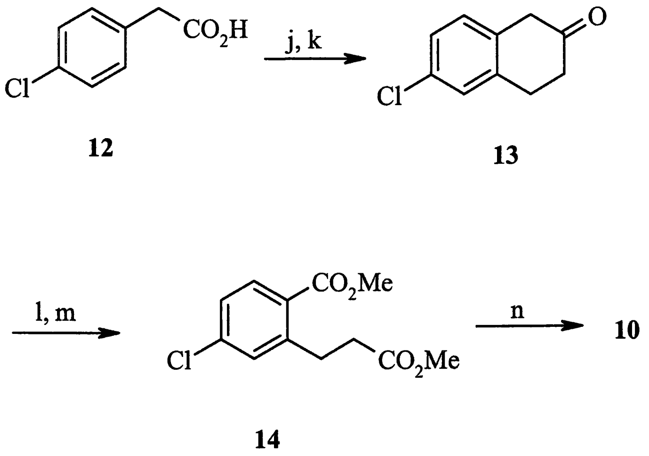
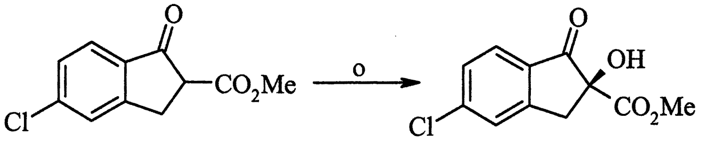

CO2H
Cl
12
j, k
O
Cl
13
l, m
CO2Me
Cl
CO2Me
14
n
10

Scheme 4. j) $SOCl_2$ *k) ethylene,* $AlCl_3$ *l)* AcO_2H*, NaOAc m) MeOH,* H_2SO_4 *n)NaOMe* dramatically reduced enantioselectivity. Many other types of chiral amines and amino-alcohols were also investigated, but to no avail. The use of chiral quaternary ammonium salts and inorganic bases failed due, apparently, to a rapid uncatalyzed background reaction. Certain chiral transition-metal complexes were found to be efficient catalysts for the hydroxylation, but no significant enantioselectivity was observed. It should be noted that the scope of this hydroxylation reaction is very limited: very little reaction occurred under these conditions for the isomeric indanones or corresponding tetralones. It should also be noted that Cinchona alkaloids are known to effect the enantioselective alkylation of 2-carbomethoxyindanone with Michael acceptors such as methyl vinyl ketone (*3*). It turns out that our observed enantioselectivity for the hydroxylation is similar to those of the Michael additions, and our observations regarding modifications of the catalyst parallel Wynberg's.



10 **(+)-11**

Scheme5. o) t-BuOOH/cat. cinchonine/PhMe/r.t.

It was found that in order to achieve high conversion with minimum catalyst-loading, *t*-butylhydroperoxide (TBHP) was superior to hydrogen peroxide (*3*). Although the reaction rate and selectivity was not strongly influenced by the choice of solvent, as long as it was anhydrous and non-nucleophilic, the use of toluene simplified the isolation of product and purification of the filtrate for use in subsequent batches. By extracting acidic byproducts from the toluene filtrates and recycling, catalyst utility was maximized. The material produced by this process in about 85% yield was approximately 45% e.e. The enantiomeric purity could be enhanced to >95% by a single recrystallization, but since a large amount of the useful enantiomer was lost to the filtrate, the 45% e.e. material was used for the subsequent steps.

To our dismay, when the enantiomerically-pure or 45%- enriched hydroxyindanone was subjected to the downstream steps, the subsequent intermediates were increasingly more difficult to isolate in satisfactorily pure form, due to the fact that the pure enantiomers were much more soluble than the corresponding racemic forms. In fact, all attempts to crystallize enantiopure indoxacarb failed during the first several months of development work. Serendipitously, hexane extraction of a highly impure solution of 45% e.e. material from a pilot-plant campaign, on prolonged standing, deposited crystals of the pure enantiomer, but this was of purely academic interest. Due to the unfavorable solubility properties of the nonracemic versions of indoxacarb and its intermediates **1** and **3**, it was necessary to redesign the downstream steps.

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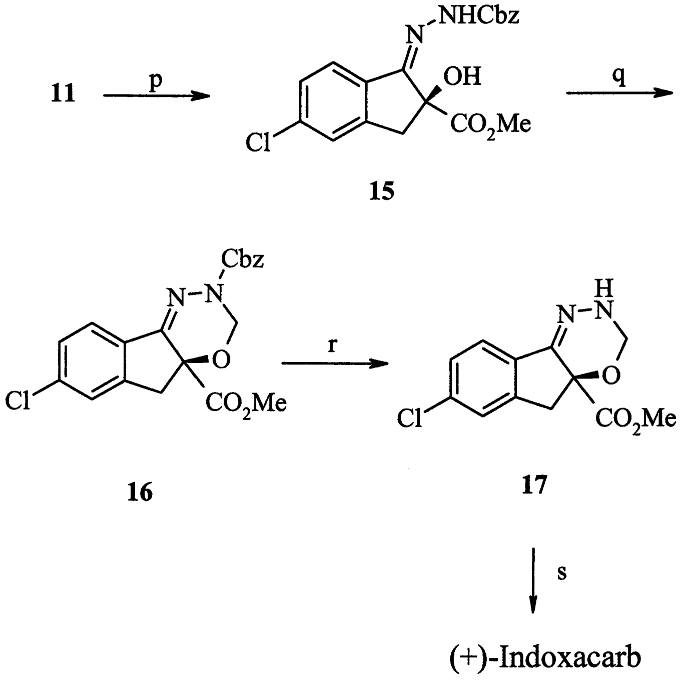

Scheme 6. p) $H_2NNHCbz$ q) $(EtO)_2CH_2/P_4O_{10}$ r) $H_2/Pd\text{-}C$ s) 2/base

Ultimately, it was found that a practical solution to the problem was to use benzyloxycarbonyl (Cbz) as a protecting group for the hydrazine moiety. This group is readily removable under mild conditions at the penultimate step, which is of prime importance, due to the relative instability of indoxacarb precursor **17**. The new strategy provided an excellent way to convert enantiomerically-enriched **11** to indoxacarb in high yield, with very little loss of material or enantiomeric purity. The new intermediates were also more soluble as the pure enantiomers than as racemates, but were sufficiently crystalline at 45% e.e. to be isolated if necessary. The new process, in addition to enabling the use of nonracemic material using very selective reactions, had the advantage of increased convergence, since the two "halves" of the indoxacarb molecule are now coupled at the very end of the sequence (*4*).

The reaction of hydroxyindanone **11** with benzyl carbazate was very clean, intrinsically more selective than the reaction with hydrazine itself, since no dimeric azine was formed. The elimination of the need to handle hydrazine and its accompanying hazardous waste-stream was an additional advantage of this process change. The crude Cbz-protected hydrazone **15** could be directly condensed with ethylal in the presence of phosphorus pentoxide and the product **16** could be isolated as a crystalline solid with negligible loss of enantiomeric excess. Debenzylation by hydrogenolysis was accompanied by decarboxylation, and the resulting unstable oxadiazine **17** was immediately coupled with carbamoyl chloride **1** to afford the desired compound. Ultimately it was found that the last two chemical steps could be combined so that the final couling could be performed "in-situ," making the process much more robust. The active non-racemic insecticide could not be isolated for the reasons described previously; thus, following extensive formulation studies, it was decided to formulate the crude final solution by deposition on a solid support. Further refinements included the replacement of the troublesome sulfur trioxide reagent and undesirable chlorinated solvent with catalytic *p*-toluenesulfonic acid and toluene, distillative removal of the alcohol co-product being the key to success *(5)*. These improvements enabled the final three steps to be carried out in a streamlined process using an inexpensive solvent (toluene, also the co-product in the hydrogenolysis step) in an overall yield of greater than 80%.

In summary, the discovery of new catalytic asymmetric oxidation chemistry and new synthetic strategies, along with meticulous process development work, enabled us to take non-racemic indoxacarb, a promising new insecticide, into the commercialization process.

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Chapter 18

Insecticidal Oxazolines

**Thomas M. Stevenson, Victor E. Amoo, George C. Chiang,
Erno Keskeny, Jeffrey K. Long, Brett A. Crouse,
Paula Sharpe, Kevin Hillegass, Latasha Jones,
and Carolyn Yatsko**

**Stine-Haskell Research Center, DuPont Crop Protection, P.O. Box 30,
Newark, DE 19714–0030**

2,4-Diaryloxazolines have very potent activity as insecticides and acaricides. We have explored the structure activity relationships on the 4-aryl ring by using palladium catalyzed cross-coupling reactions of a 4-(4-iodophenyl)oxazoline. Highly active novel oxazolines were produced from Sonogashira, Suzuki, Heck, Negishi, and Stille reactions. Highest levels of activity were observed with phenylacetylene substituents. Field testing against Spodoptera and Tetranychus species of optimal compunds revealed activity at rates as low as 10 -25 g/Ha.

Introduction

Several years ago Yashima reported that 2,4-Diaryloxazolines such as etoxazole **1** have very potent activity as insecticides and acaricides (*1*). A key structural feature important for activity was the presence of 2,6-disubstitution on the 2-aryl ring (Figure 1). A wide variety of substituents on the 4-aryl ring were reported to be possible. On closer inspection only a small percentage of the

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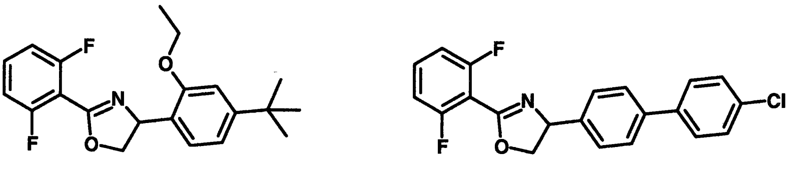
disclosed compounds had good activity on lepidopteran insects, but nearly all possessed very impressive activity on various mite species. Our interest in trying to find novel oxazolines hinged on discovering compounds that had both insecticidal and acaricidal activity. Of the compounds that had lepidopteran activity, many were biphenyls like **2**. Thus, we chose to begin with the 4-biphenyloxazolines as a starting point for proprietary chemistry.



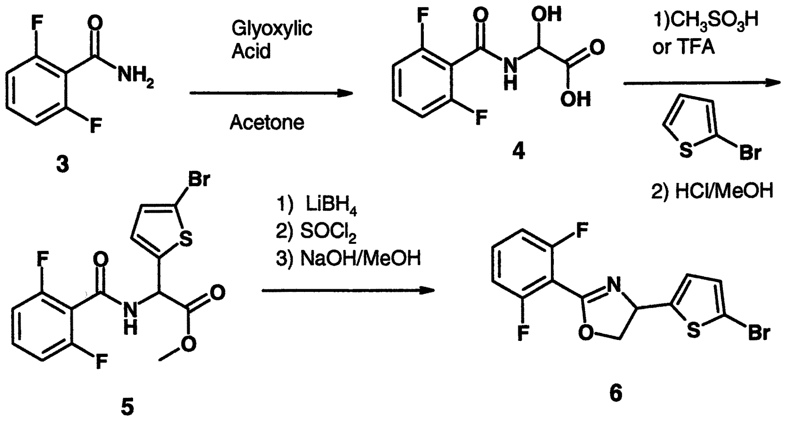
1
Etoxazole Miticide

2
Miticide and Insecticide

Figure 1. 2,4-Diaryloxazoline Insecticides

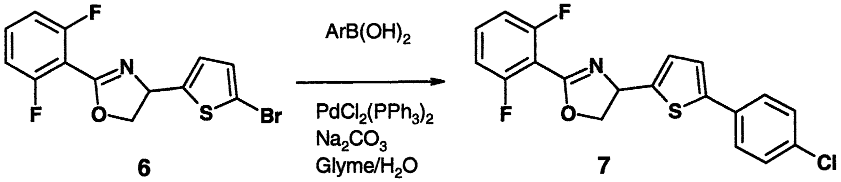
Thiophene Containing Biaryls

Replacing one ring in the biphenyl oxazolines with a thiophene was our initial synthetic goal. To get to biaryls with a thiophene proximal ring we needed to discover a way to quickly make thienyl glycines. Ben-Ishai discovered a useful way to make protected phenylglycines by amidoalkylation chemistry (*2*) using hydroxyhippuric acid with activated aromatics. Thiophenes are more activated to electrophilic substitution than typical aromatics so this type of approach appeared feasible. Since the most active oxazolines contain a 2-(2,6-difluorophenyl)ring we decided to make a 2,6-difluoro version of hydroxyhippuric acid **4** for use in amidoalkylation reactions. Thus, our "protecting group" would become part of the final product (Scheme 2). The amidoalkylation agent was prepared by reacting glyoxylic acid with 2,6-difluorobenzamide **3**. Reaction of **4** in methanesulfonic acid or trifluoroacetic acid as solvent with various substituted thiophenes produced thienyl glycines like **5** containing all the necessary atoms for the contruction of the final oxazolines. The crude acids were converted to methyl esters to simplify reduction to primary alcohols with lithium borohydride solution. Ring closure to, for example, **6** was carried out by chlorination with thionyl chloride and cyclization with methanolic sodium hydroxide.


F
O
NH2
F
3
Glyoxylic Acid
Acetone
F
O
OH
N
H
O
OH
F
4
1)CH3SO3H or TFA
S
Br
2) HCl/MeOH
Br
S
F
O
N
H
O
O
F
5
1) LiBH4
2) SOCl2
3) NaOH/MeOH
F
N
F
O
S
Br
6

Scheme 1. Amidoalkylation with 2,6-Difluorohippuric Acid

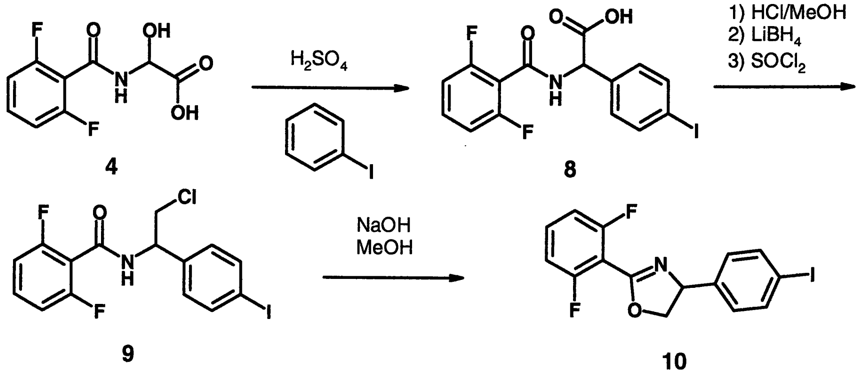
We prepared **6** by this method on a relatively large scale to use in the preparation of thiophene analogs of the biphenyloxazolines. As shown in Scheme 2, the Suzuki coupling reaction with boronic acids allowed us to prepare a wide variety of 5-phenylthiophene containing final products such as **7**. These compounds showed outstanding miticidal activity, but had relatively weak activity on lepidopteran pests (*3*). We therefore turned our attention to other targets. Oxazoline **7** exhibited two spotted spider mite larval control at 0.1 ppm.


F
N
F
O
S
Br
6
ArB(OH)2
PdCl2(PPh3)2
Na2CO3
Glyme/H2O
F
N
F
O
S
Cl
7

Scheme 2. Thiophene Isosteres of 4-Biphenyloxazolines

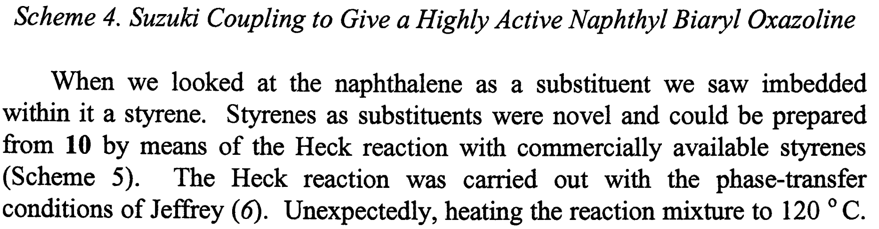
Naphthyl and Styryl Containing Oxazolines

The versatility of **6** led us to want to make a phenyl version of this to allow substitution of the distal ring of the biphenyl with novel replacements (Scheme 3). However, when we tried our amidoalkylation strategy on iodobenzene with trifluoroacetic acid as solvent we isolated very little phenylglycine product. Switching to concentrated sulfuric acid gave the amidoalkylation product **8**, along with a minor *ortho*-iodophenyl byproduct. The reduction and cyclization of **8** gave the key 4-(4-iodophenyl)oxazoline **10**. The sequence to our key intermediate was carried out without need for chromatography and could be done up to kilogram scale.



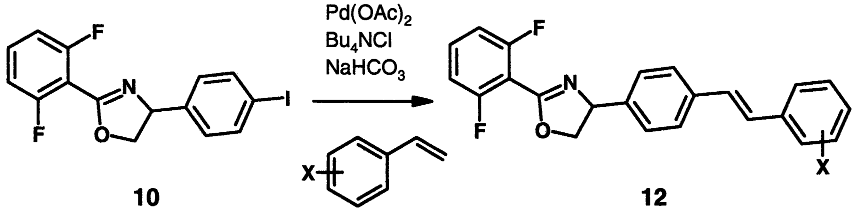
Scheme 3. Amidoalkylation Route to a 4-(4-Iodophenyl)oxazoline

We carried out a variety of boronic acid coupling reactions with **10** to give biphenyloxazolines with novel substituents such as nitriles, esters, oximes and aldehydes (*4,5*). While many of them showed interesting activity, the Suzuki coupling product **11** of 2-naphthylboronic acid stood out because it suggested that larger structural changes could be made while retaining activity (Scheme 4). In particular, **11** had excellent efficacy on mites, but also showed activity on several lepidopteran pests at 2 ppm.



Scheme 4. Suzuki Coupling to Give a Highly Active Naphthyl Biaryl Oxazoline

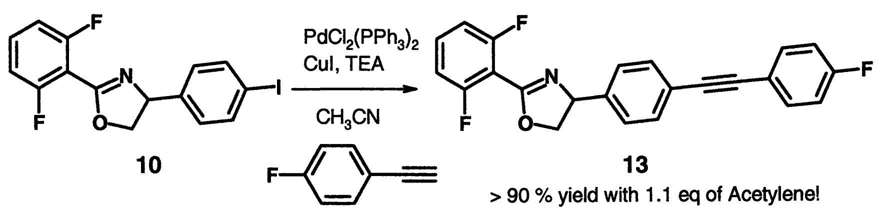
When we looked at the naphthalene as a substituent we saw imbedded within it a styrene. Styrenes as substituents were novel and could be prepared from **10** by means of the Heck reaction with commercially available styrenes (Scheme 5). The Heck reaction was carried out with the phase-transfer conditions of Jeffrey (*6*). Unexpectedly, heating the reaction mixture to 120 ° C. was necessary to complete the reaction. We investigated a variety of different styrenes and produced stilbenes **12** which gratifyingly exhibited broad spectrum activity (*4*). Highest activity was shown by the product of 4-chlorostyrene. The compounds showed such good levels of activity (lepidopteran activity at 1-2 ppm and mite activity at < 0.1 ppm) that they were evaluated in field trials. However, they were quickly degraded by sunlight and showed less than expected efficacy in these trials.



Scheme 5. Styryloxazolines from the Heck Reaction

Acetylene Spaced Oxazolines

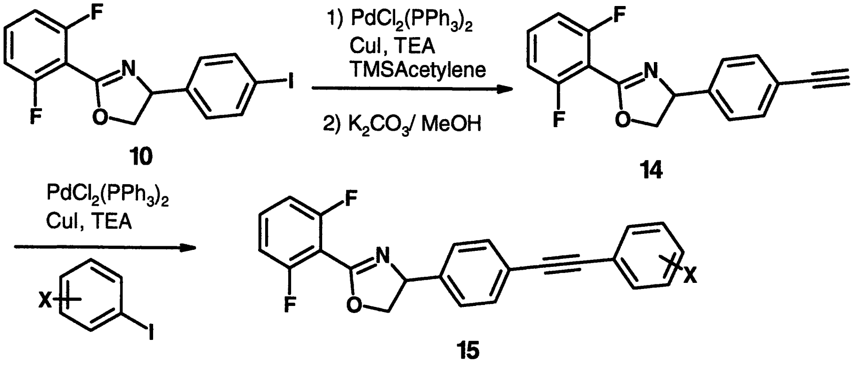
In order to regain some of the photostability necessary for field potency, but retain the 2 atom spacer we turned to aryl acetylenes as substituents (Scheme 6). The well known Sonogashira coupling reaction (*7*) of acetylenes and aromatic halides is especially facile with aromatic iodides. Oxazoline **10** was no exception and reaction with phenylacetylene under palladium and copper co-catalysis proceeded at room temperature in excellent yield. The product showed unusually high levels of activity on lepidopteran pests and on mites (*4*). Sonogashira coupling of **10** with 4-fluorophenylacetylene gave oxazoline **13** which showed even higher levels of activity. Control of lepidopteran species at below 1ppm and spider mite larvae below 0.01 ppm was observed with **13**.



Scheme 6. Sonogashira Coupling

Such high levels of activity warranted a large follow-up program. There were very few commercially available arylacetylenes and we wished to avoid preparing them. Therefore, we sought to make an oxazoline aready containing the acetylene which could be coupled with commercially available aryl iodides. Sonogashira coupling of **10** with trimethylsilyl acetylene and deprotecting with methanolic potassium carbonate produced the requisite ethynyloxazoline **14**.

Coupling chemistry with a variety of aryl iodides allowed swift preparation of substituted ethynyloxazolines **15** (Scheme 7).

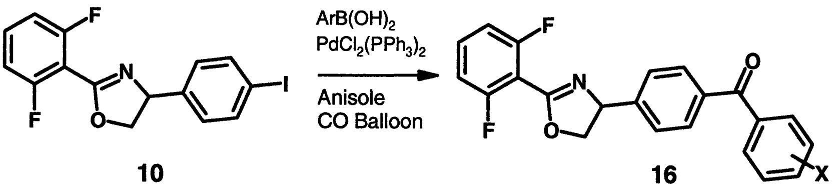


Scheme 7. Analoging Strategy for 4-(4-Arylacetylene)oxazolines

In addition to the aryl acetylenes we also carried out Sonogashira chemistry of **10** with many commercially available non-aromatic acetylenes. Excellent activity on both lepidopteran pests and mites was seen for Sonogashira products of acetylenes substituted with silyl, alkyl, and acetal substituents (*4,8*). Especially interesting broad spectrum activity was exhibited by the product from t-butylacetylene which controlled lepidopteran larvae at 2 ppm.

Carbonyl Spaced Oxazolines

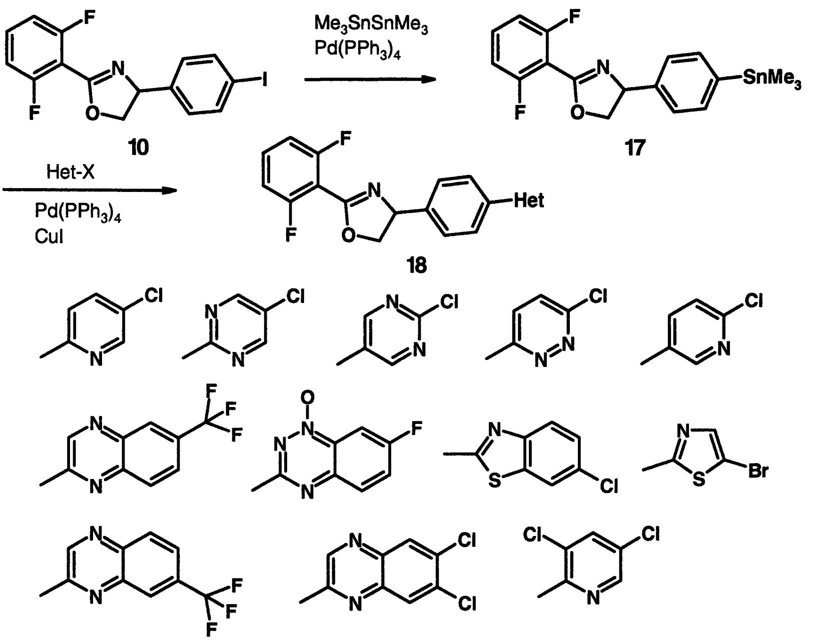
Palladium chemistry allowed us to quickly evaluate various 0- and 2-atom linkers, but we still wished to pursue synthesis of 1-atom linkers. Miyaura and Suzuki reported (*9*) that boronic acid coupling reactions done in the presence of carbon monoxide could convert iodides to benzoyls in good yield. Carrying out the Miyaura-Suzuki couplings with **10** in anisole under a balloon of carbon monoxide gave benzoyloxazolines **16** with a variety of different arylboronic acids (Scheme 8). However, they only had high levels of activity against mites.



Scheme 8. Miyaura-Suzuki Carbonylative Coupling Chemistry

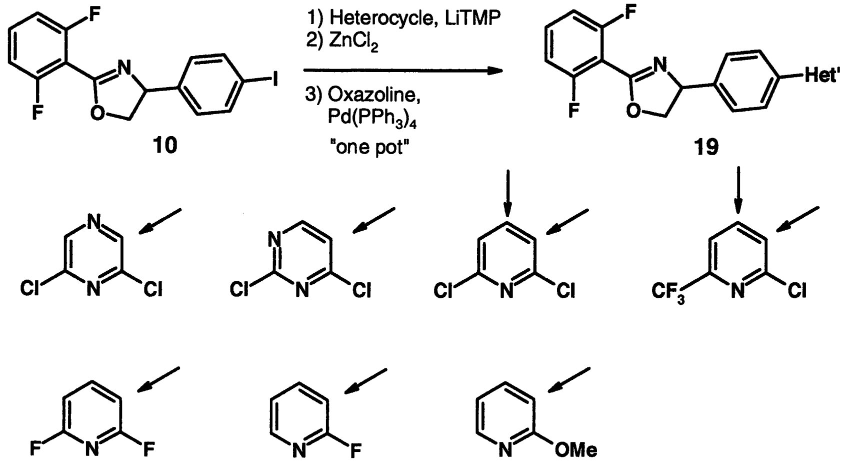
Heterobiaryl Oxazolines

Our previous results predicted that compounds with heterocycles as distal rings might have high levels of broad-spectrum activity. In order to use readily available heterocyclic halides as coupling partners, we needed to convert the oxazoline into an organometallic reagent. Stille coupling of **10** with a distannane proved to be an excellent reaction to give the stannyloxazoline **17**. Stannane **17** when coupled with a large number of different halides gave heterobiaryl oxazolines **18** (Scheme 9). Highest activity was observed for pyridines and quinoxalines on both lepidopteran insects and mites. All of the compounds prepared, even the benzotriazole-N-oxide product, exhibited good insecticidal activity.



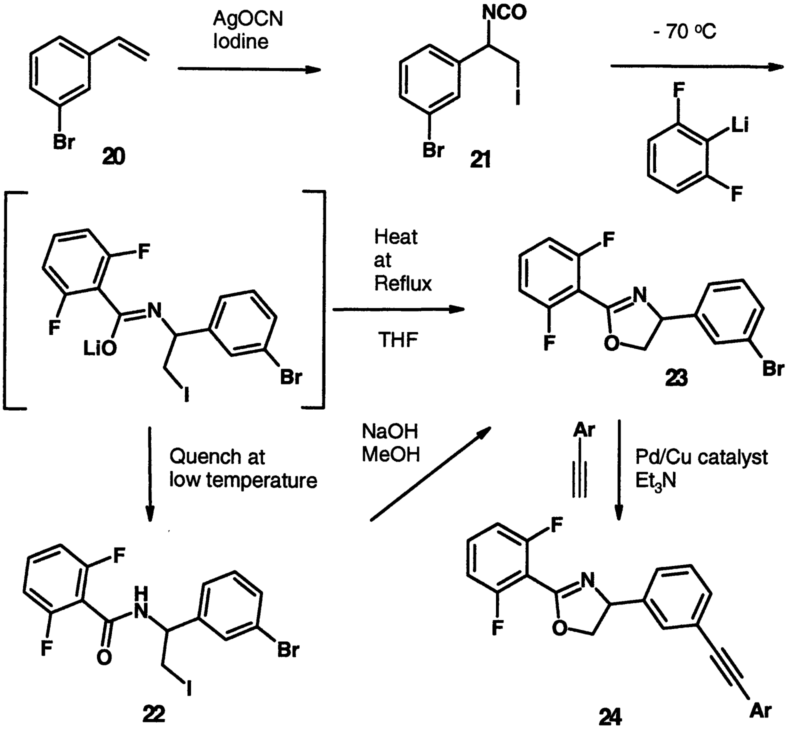
Scheme 9. Stille Coupling Strategy for Distal Heterobiphenyl Analogs

The work of Queguiner and others (*10*) on the metallation of pyridines and diazines suggested a way to make compounds in which the corresponding heterocyclic halide was not readily available. For example, reaction of 2,6-dichloropyrazine with lithium tetramethylpiperidide gave a 3-lithiopyrazine which smoothly coupled with **10** after transmetallation with zinc chloride. This Negishi coupling strategy provided a variety of heterocyclic oxazolines **19** with substitutents in the *ortho*-position of the distal ring. The position of lithiation and subsequent coupling is indicated by the arrows in Scheme 10.



Scheme 10. Negishi Coupling with Heteroaromatic Zinc Reagents

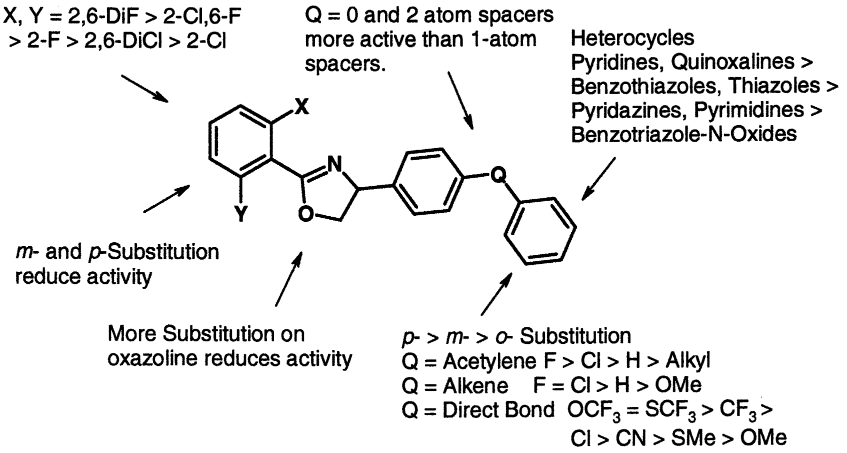
Our analoging strategy based on products of amidoalkylation was very convenient, but the electrophilic nature of the reaction left us with only *ortho-* and *para*-substituted products. In order to assure ourselves that we had investigated the area thoroughly enough we needed to prepare compounds with *meta*-substitution. This required another method to make oxazolines not based on electrophilic substitution chemistry. We settled on a strategy based on the work of Heathcock and Hassner (11) who showed that styrenes readily add *in-situ* generated iodoisocyanate (Scheme 11). If the intermediate beta iodoisocyanates would react with lithium reagents at the isocyanate function, the intermediate amides might cyclize to oxazolines either directly or in a subsequent reaction with base. Reaction of 3-bromostyrene **20** with iodine and silver cyanate gave the expected iodoisocyanate **21**. Indeed, reaction at low temperature with 2,6-difluorophenyllithium gave an intermediate which cyclized to oxazoline **23** upon heating the reaction mixture. Hydrolysis of the reaction gave iodoamide **22** which cyclized with methanolic sodium hydroxide to **23** in even higher overall yield. Sonogashira reaction of **23** with arylacetylenes gave the previously elusive *meta*-substituted acetylenic oxazolines **24**. However, the activity of these compounds was far lower than that seen for *para*-substituted oxazolines. This useful and general methodology allowed us to make a wide variety of oxazolines from both styrenes and other alkenes.


AgOCN
Iodine
NCO
I
Br
20
21
- 70 °C
F
Li
F
LiO
N
Br
Heat
at
Reflux
THF
O
23
Quench at
low temperature
NaOH
MeOH
Ar
Pd/Cu catalyst
Et_3N
H
22
24
Ar

Scheme 11. Novel Oxazoline Synthesis via Styrenes

Structure-Activity Relationships

The compounds described in this chapter had extremely high levels of activity on lepidopteran insects such as Fall Armyworm, Beet Armyworm, Diamondback Moth and Cabbage Loopers with even more impressive activity on various Tetranychus and Panonychus mite species. These oxazolines act as insect growth regulators and activity is only expressed on larval stages. Adult insects and mites are not controlled by oxazolines. The activity ratings on insects were read at 96 hours or later in order to measure full effect. Some aspects of structure activity relationships are shown in Figure 2.



X, Y = 2,6-DiF > 2-Cl,6-F > 2-F > 2,6-DiCl > 2-Cl

Q = 0 and 2 atom spacers more active than 1-atom spacers.

Heterocycles
Pyridines, Quinoxalines > Benzothiazoles, Thiazoles > Pyridazines, Pyrimidines > Benzotriazole-N-Oxides

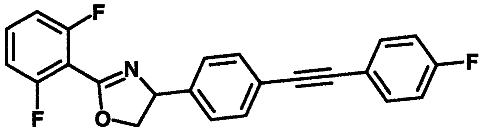
m- and *p*-Substitution reduce activity

More Substitution on oxazoline reduces activity

p- > *m*- > *o*- Substitution
Q = Acetylene F > Cl > H > Alkyl
Q = Alkene F = Cl > H > OMe
Q = Direct Bond $OCF_3 = SCF_3 > CF_3 >$ Cl > CN > SMe > OMe

Figure 2. Some Aspects of Structure-Activity Relationships

Extensive studies in the greenhouse established DPX-KY422 **13** (Figure 3) as our most active broad spectrum insecticide. Worldwide field testing of this compound showed it to be very effective as both an acaricide and lepidopteran insecticide. DPX-KY422 controlled spider mites at rates as low as 10 g/hl. in orchard tests. Rates of 25-100 g/ha. gave good control of various Spodoptera species on vegetables.



13

Figure 3. DPX-KY422: Broad Spectrum Insecticide/Acaricide

Conclusions

Palladium catalyzed cross-coupling reactions provided a very convenient and divergent route for synthesizing a broad range of oxazoline insecticides. The compounds disclosed in this chapter are extremely effective acaricides which are toxic to spider mite larvae at rates well below 1 ppm. Compounds with 0- and 2-atom spacers generally showed high activity against lepidopteran pests with optimal activity also well below 1 ppm for many species. Unexpectedly, carbonyl spaced and thiophene containing oxazolines retained high activity only on mites.

Acknowledgements

We would like to thank the following entomologists for their excellent collaboration and for running both laboratory and field trials: Jim Gilmour, Dave Marsden, Chris Clark, John Nogaj, Shelley Hunt, Ray Yarnall, Bruce Stanley, Johannes Busch and Steve Irving. Process studies and large scale syntheses of intermediates were carried out by Steve Hartzell, Julius Fuchs, Gary Annis, Jim Zerbe and Paul Manchester. Analytical support of this project was provided by Dan Linn, Paul Tseng, Gina Blankenship and John Groce.

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Chapter 19

Discovery of the Indolebenzhydrylpiperazines and Benzhydrolpiperidines: A New Class of Insecticides

John W. Lyga, I. Robert Silverman, Syed F. Ali, Thomas G. Cullen, Daniel H. Cohen, and Kirk A. Simmons

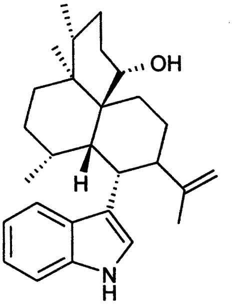
Discovery Research Department, Agricultural Products Group, FMC Corporation, P.O. Box 8, Princeton, NJ 08543

The indolebenzhydrylpiperazines and benzhydrolpiperidines are a new class of insecticides that were discovered while optimizing activity of the natural product lead, 10,23-dihydro-24,25-dehydroaflavinine (**1**) and a closely related natural product, nominine (**2**). Synthesis directed at simplifying the natural product lead resulted in the discovery of the tryptamine analogs **3** and **4**, which were both weakly active in a voltage-gated calcium channel assay. A hybrid molecule, the indolebenzhydrylpiperazine (**7**), containing features of **4** and the calcium channel drug, cinnarizine (**6**), had foliar activity against cabbage looper and tobacco budworm. Optimization of the second-generation lead resulted in the discovery of the benzhydrolpiperidines (**8**), which are potent lepidoptericides acting at the voltage-gated sodium channel.

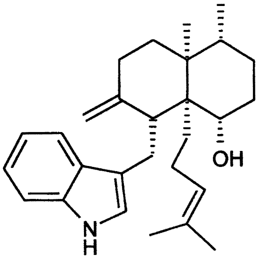
In the early 1990's, FMC collaborated with Xenova, LTD (1) to screen fermentation extracts against a battery of *in vitro* target site assays for the discovery of novel insecticide leads. One indole-containing fungal metabolite,

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

10,23-dihydro-24,25-dehydroaflavinine (**1**), was weakly activity in a nicotinic acetylcholine receptor (nAchR) assay. A search of the literature for closely related indole containing natural products led us to nominine (**2**) due to the reported activity against *Heliothis zea* (2). Nominine and dihydrodehydroaflavinine are closely related indole diterpenes, each having a similar carbon skeleton consisting of an indole ring attached at the 3-position to a cis-fused decalin system with a pendant side chain at the ring junction. In comparing the common features of the natural product lead (**1**) with the insect active nominine, we found that there is good overlap between the indole and cis-decalin portions of the two molecules (Figure 1)(3). The prominent angular side chain in



10,23-dihydro-24,25-dehydroaflavinine (1)



nominine (2)

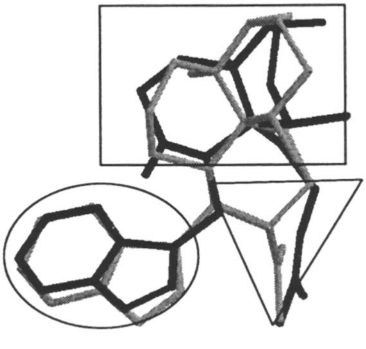
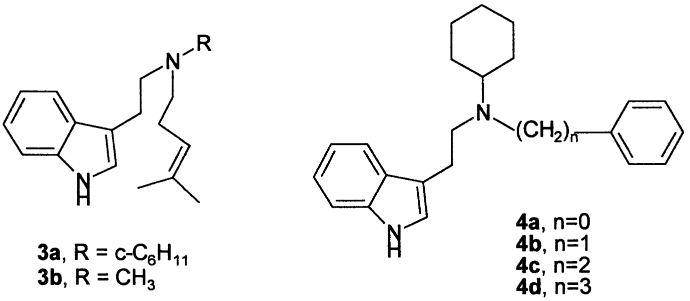


Figure 1. Overlay of compound 1 (gray) and compound 2 (black); oval: indole rings; rectangle: cis decalin rings; triangle: angular side chain.

nominine is conformationally restricted in **1**. Our optimization strategy for the natural product lead **1** was based on the combined features of **1** and **2**. Our goal was to retain the indole ring and side chain and replace the complex lipophilic scaffold with a simplified bioisostere. We directed our initial synthetic efforts at designing simpler structures that fill the volumes occupied by the cis-decalin and still allow the indole rings and side chains of the designed structures to overlap with features of **1** and **2**.

In looking for scaffolds that could be modified to occupy both the cis-decalin and the alkenyl side chain independently, we selected tryptamine. This allowed us to readily attach two different substituents to the primary amine; one to replace the decalin ring and one for the pendant side chain. The first two compounds prepared were the N-cyclohexyl (**3a**) and N-methyl analogs (**3b**) (Figure 2). Both analogs were the first simplified indoles to have activity in an *in vivo* screening assay at 100 μM against yellow fever mosquito (YFM) and



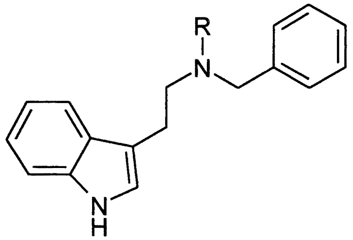
3a, R = c-C_6H_{11}
3b, R = CH_3

4a, n=0
4b, n=1
4c, n=2
4d, n=3

Figure 2. Early tryptamine analogs

activity in the nAchR assay. With this encouraging result, we prepared isosteric replacements for the pentenyl group as well as other R group replacements beside methyl and cyclohexyl. We started by replacing the pentenyl group with a phenyl. We postulated that the phenyl group would provide the unsaturation, yet be less vulnerable to metabolic deactivation. Benzyl, phenethyl and phenylpropyl analogs were also prepared to vary the distance between the phenyl and the nitrogen. None of the new analogs (**4a** – **4d**) were active against YFM nor were they active in the nAChR assay. The N-benzyl analog **4b**, however, was active in a new assay we had developed, a voltage-gated calcium channel assay (4). Interestingly, a number of the tryptamine analogs were also showing weak activity in this assay.

Using N-benzyltryptamine as the new lead we prepared a factorial design set of cyclohexyl replacements varying the lipophilic (π), electronic (σ*), and



Factorial Set

R = CH_2OCH_3, CO_2Et, C_2H_5,
C_6H_5, PO_3Et_2, NHC_4H_9,
CH_2Ph, CH_2-c-propyl,
cyclohexyl, $NHCH_3$,
$NHCSNH_2$

Figure 3. N-benzyltryptamine design set

steric (MR) properties (Figure 3). Although all analogs had activity at the micromolar level in the calcium channel assay, none were more active than the cyclohexyl lead. Because of the activity that we were observing in the calcium channel assay, we did a literature search to find compounds that act at the voltage-gated calcium channel. The one that appeared structurally similar to the N-benzyl-N'-cyclochexyltryptamine, was the piperazine compound, cinnarizine

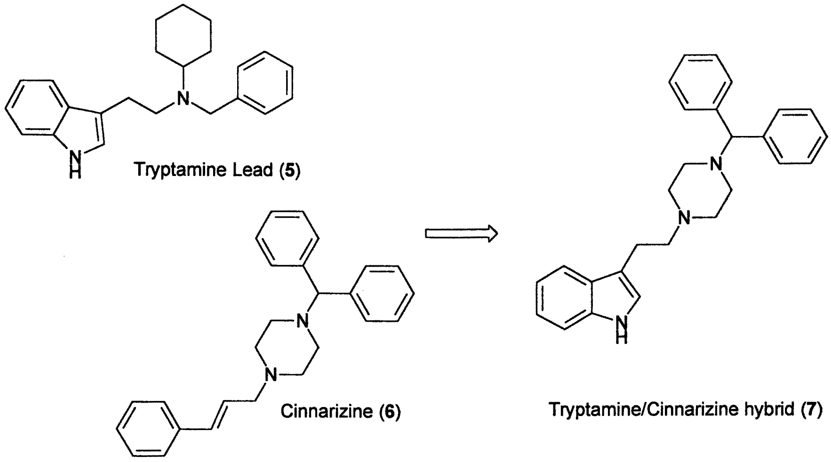


Figure 4. Indolebenzhydrylpiperizines; a tryptamine/cinnarazine hybrid

(6) (Figure 4). We postulated that the cinnamyl portion of cinnarizine might be isosteric with our indole ring. Both compounds have a nitrogen atom roughly the same distance from the center of the phenyl ring. The benzhydryl group in cinnarizine could also be viewed as a lipophilic isostere for the decalin ring and the side chain of nominine. We tested cinnarizine in a lepidopteran screening assay using cabbage looper and found it to be active at 300 μM, unlike our tryptamine analogs that were inactive. We synthesized a cinnarizine/indole hybrid structure (7), replacing the cinnamyl portion of cinnarizine with an indolealkyl group. Compound **7**, the indolebenzhydrylpiperazine (IBP), was found to be significantly more active against cabbage loopers than cinnarizine (IC_{50} = 30 uM) while retaining activity in the calcium channel assay.

As a starting point for optimization of the new IBP lead, we divided the core structure into four subsections; the indole, the tether, the piperazine ring, and the benzhydryl group (Figure 5). Our first synthetic moves were to probe substitution in the indole ring, vary the tether length, modify the piperazine, and explore substitution in the benzhydryl. For the initial targets, we chose to use the unsymmetrical benzhydryl ring having a 4-chloro on one of the rings. We found that the length of the carbon tether had a large impact on insecticidal activity. The one or two-carbon tether had a similar effect against cabbage looper whereas the three-carbon tether was inactive (Figure 6). When the benzhydryl was substituted with a bis-4, 4'-chloro or bis-4, 4'-OCF_3 group, the one carbon tether was slightly more active than the two-carbon tether. We chose to keep the tether length fixed at one carbon for the duration of optimization.

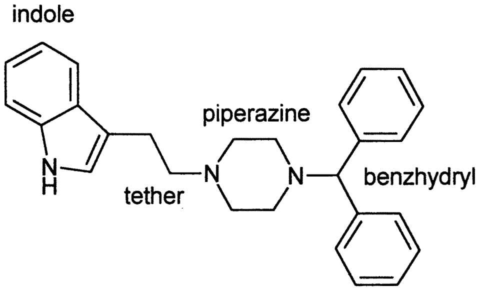
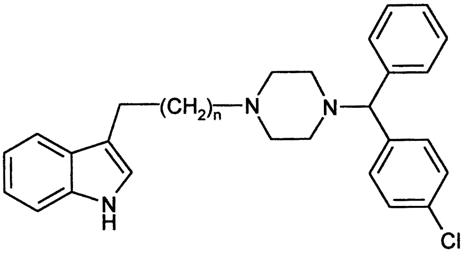


Figure 5. Optimization strategy for the IBP's

A series of monochloroindoles was prepared to probe substitution in the indole ring; the 4-chloro was found to be the most active but not significantly more active than H. This position was optimized by synthesizing a factorial design set of compounds varying the physiochemical properties π, σ-para, and MR. The more active substituents were H, NO_2, F, and OCH_3. In addition to the activity against cabbage looper, these new analogs were also providing contol of tobacco budworm (TBW) at 10μM in a diet incorporated assay. The 4-fluoro analog was the most active against TBW. Substitution at the bridging carbon between the indole and piperazine with methyl, n-hexyl, cyclopropyl, and phenyl (Figure 7) all resulted in reduced activity against TBW. Likewise, expanding or contracting the piperazine ring (m=2, n=3; m=2, n=1; m=3, n=1) all resulted in reduced activity. A number of substituted benzhydryl analogs



n (X=H)	*%control of cabbage looper at 100 μM*
0	75
1	89
2	0

Figure 6. Effect of tether length on cabbage looper diet activity

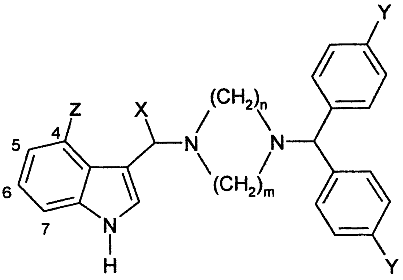
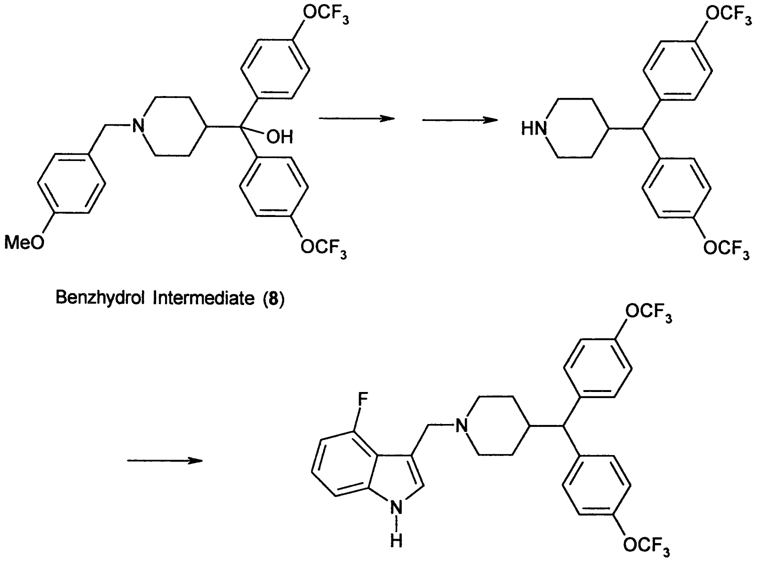


Figure 7. Optimization of the IBP's

were prepared, none were more active than the bis 4,4'-OCF_3 analog. The most active piperazine analog from the initial optimization, Z=F, X=H, and Y=OCF_3, provided 50% control of TBW in a foliar assay at 26 ppm.

Since small changes to the piperazine ring had a large effect in insect activity, we decided to determine the importance of the piperazine nitrogens by preparing both deazapiperazine analogs. We started by synthesizing the N-(indolemethyl)piperidine (**9**) (Figure 8). We chose to use the methoxybenzyl group as a piperidine protecting group for the construction of the benzhydrol-piperidine and then attach the indole as the last step. The "protected" benzhydrol intermediate (**8**) was screened in our TBW diet assay and found to be very active. The benzhydrol intermediate had similar TBW diet activity as the IBP's but was a full order of magnitude more potent in a topically applied assay. It was the improved topical activity that led us to pursue the optimization of the new benzhydrolpiperidine lead (BZP) over the IBP's.

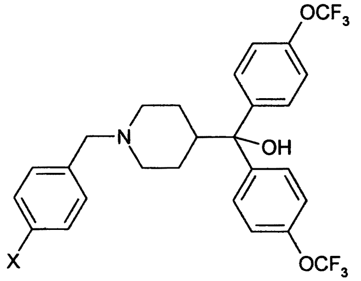


Benzhydrol Intermediate (**8**)

Indolemethyl piperidine target (**9**)

Figure 8. Synthesis route for the deaza target

Initial optimization of the BZP's indicated the benzyl ring para position could tolerate a variety of substituents and still maintain high levels of TBW activity. The more potent analogs have para substituents that span a range of electronic and lipophilic physiochemical properties while having very similar steric properties (Figure 9). One property in common with the set of the more active analogs is that all have H-bond accepting groups. Substitutions at the benzyl ortho and meta positions generally lead to reduced activity. Modification of the rest of the BZP structure can be summarized as follows:



X	π	σ	*L*	B_l	B_5
O-cyclopropyl	0.89	-0.24	6.48	1.35	3.16
CO_2iPr	0.81	0.48	6.18	1.64	4.40
$NHCO_2Et$	-0.38	-0.17	6.81	1.45	3.60

L = length, B_l = minimum radius, B_5 = maximum radius

Figure 9. Benzyl para position active substituents

The piperidine ring appears to be optimum, increasing or decreasing the length between the benzhydrol and benzyl or changing the ring size reduces activity. Acyclic analogs are generally less active than cyclic analogs (Figure 10). N-Oxidation of the piperidine usually maintains or enhances insecticidal activity. The benzhydrol OH group is important for activity. Replacement of the benzhydrol OH by H or F reduces the TBW activity, but not as much as expected if H-bond donation or acceptance is critical. The reduction in TBW activity observed by replacement of OH by SH and methoxy suggests a possible steric influence, possibly affecting the orientation of the benzhydrol phenyl rings. The para substituted benzhydrol is optimum, 4-CF_3 or 4-OCF_3 is best, although one of the phenyl rings can be replaced with smaller groups and still maintain activity. The insecticidal activity of our initial optimized structures against a variety of insect pests is shown in Figure 11. In general, the BZP's are effective lepidoptericides equivalent to cypermethrin in the laboratory. They

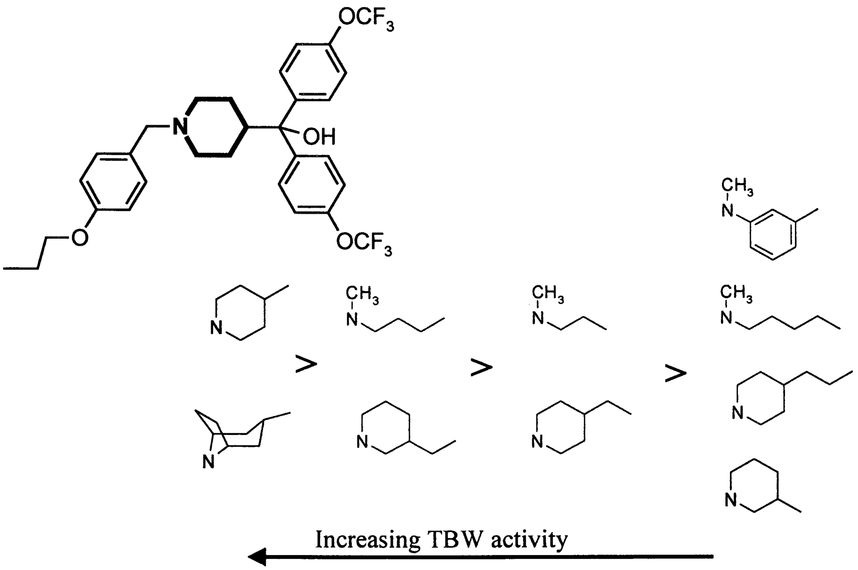
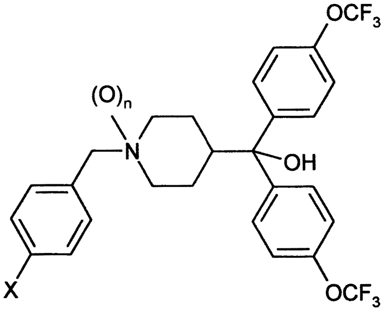


Figure 10. Effect of piperidine modifications on TBW activity

act mainly through ingestion and have limited contact activity. Insects become paralyzed between 1-2 days after feeding and die within 3-4 days.

Mechanism of Action

As mentioned earlier, the indole lead was a hybrid structure based on the calcium channel blocker cinnarizine. In addition to being active at the calcium channel, cinnarizine is also active at the voltage-gated sodium channel. We noticed that symptoms of insects treated with the IBP's and BZP's were similar to the symptoms produced by pyrazolines. The BZP's cause treated TBW to curl up and not move. When probed, they are not hyperactive nor progress into spontaneous convulsions like insects treated with DDT. Neurophysiological studies on TBW treated with BZP's indicate a reduction in CNS activity with little or no change in motor neuron activity. This is similar to the neurophysiological effect reported for pyrazolines. Like cinnarazine (5), the pyrazolines also act at both the voltage gated sodium channel and calcium channel (6-9). The IBP's and BZP's were subjected to biochemical and



X	n	Foliar LC_{50} (ppm)						
		BAW	CL	TBW	CEW	SBL	FAW	MBB
$NHCO_2CH_3$	0	5	3	7	7	13	4	>100
$NHCO_2CH_3$	1	7	4	6	<3	6	0.7	>200
cypermethrin		6	1	4	3	3	<3	<1
bifenthrin		2	0.4	2			2.7	0.1

BAW = beet armyworm , CL = cabbage looper , TBW = tobacco budworm, CEW = corn earworm, SBL = soybean looper, FAW = fall armyworm, MBB = mexican bean beetle

Figure 11. Laboratory activity of the optimized BZP.

pharmacological *in vivo* testing (10). The major effects were observed to be at the sodium channel with minor effects at the calcium channel. Ion flux experiments carried out by Prof. J. Bloomquist (11) confirmed that the IPB's and BZP's are more active at the sodium channel than at the calcium channel.

Conclusion

The natural products 10,23-dihydro-24,25-dehydroaflavinine (**1**) and nominine (**2**) were used as the starting point for optimization of insecticidal activity. After a combination of targeted design strategies and serendipitous discoveries we identified a new lead, the tryptamine analog **5**. Compound **5** was found to have activity in our calcium channel receptor assay and possess weak activity against yellow fever mosquito. While optimizing the activity of **6**, we prepared hybrid structures combining features of the tryptamine with known calcium channel receptor agonists and antagonists. Through this effort, we identified a new class of compounds, the indolebenzyhydrylpiperazines (IBP's), having lepidoptericidal activity. Further exploration of the pharmacophore led to the more potent benzhydrolpiperidines (BZP's). The IPB's and BZP's are neurotoxins which, we believe, are acting primarily at the voltage-gated sodium channel. They act on the larval stage primarily through ingestion, providing lab efficacy on lepidoptera comparable to that of cypermethrin.

Acknowledgments

The authors are indebted to Katherine G. Anouna, David J. Kerwick, Susan Beresnyak, David S. Rosen, Charles A. Webster, and Dr. Stephen W. Szczepanski for synthesis of many of the compounds; to Drs. Phillip A. Cruickshank and David M. Roush for the modeling work with structures 1, 2, and 3; to Drs. I. M. Abalis, Jane P. Breen, Greggory T. Payne, Joel M. Wierenga, and to Lyle P. Kinne, F. Larry Marek, M. Joan Plummer for the biological testing, and to Drs. Jane A Dybas, Angelina J. Duggan, and William A. Van Saun for their managerial leadership.

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Chapter 20

Insecticidal *N*-Arylalkyl-4-benzhydrolpiperidines: Optimization of the Benzhydrol Region

Robert N. Henrie II, Syed F. Ali, Katherine G. Anouna, Thomas A. Bara, Edward J. Barron, John W. Buser, Daniel H. Cohen, Philip A. Cruickshank, Thomas G. Cullen, Mary E. Ditolvo, Jane A. Dybas, David J. Kerwick, Louis V. LaFrance, David C. Lloyd, John W. Lyga, Michael J. Manning, Francis L. Marek, Alexander C. Oliphant, Clinton J. Peake, M. Joan Plummer, David S. Rosen, Elizabeth G. Rowley, I. Robert Silverman, Stephen W. Szczepanski, Michael A. Walsh, Charles A. Webster, and Joel M. Wierenga

Discovery Research Department, Agricultural Products Group, FMC Corporation, P.O. Box 8, Princeton, NJ 08543

The benzhydrol region of an insecticidal N-arylalkyl-4-benzhydrolpiperidine lead was optimized for insecticidal potency using *in vivo* data. Preliminary probing of aromatic ring positions and bioisosteric substitutions confirmed the benzhydrol framework to be optimal. QSAR and CoMFA confirmed the optimal *para*-substituents to be CF_3 and OCF_3. In this case our lead already contained the optimal groups.

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

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N-Arylalkyl-4-benzhydrolpiperidines, commonly referred to as "BZP's"-an acronym taken from "**B**en**Z**hydrol **P**iperidines"-constitute a new class of lepidoptericides that was discovered at FMC several years ago (*1*). This paper describes the optimization of the benzhydrol, or diarylcarbinol, end of the molecule (*2*). T.G. Cullen, et al, have presented the optimization of the arylalkyl domain on the opposite end of the molecule (*3*).

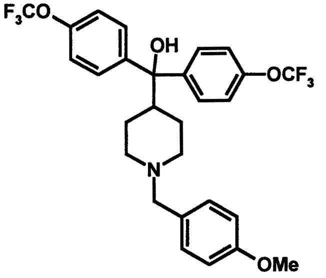
Lead Molecule

Our lead structure in the BZP chemistry was a synthesis intermediate from another insecticide program, and was identified by *in vivo* screening against tobacco budworm (TBW). The initial lead was actually quite active, with an incorporated DIET pI_{50} value of 6.1 for weight inhibition, and FOLIAR TBW LC_{50} value of 59 ppm (Table I). Other lepidoptera were also susceptible to this chemistry as exemplified by beet armyworm. Insecticidal potency was optimized using the TBW incorporated DIET test, followed by FOLIAR evaluation of the most potent analogs. Table 1.

Table I. Initial Lead Activity

Test	*Activity*
TBW Diet	$pI_{50} = 6.1$
	$pLD_{50} = 4.6$
TBW Foliar	LC_{50} = 59 ppm
BAW Foliar	LC_{50} = 81 ppm

TBW = tobacco budworm, *Heliothis virescens*
BAW = beet armyworm, *Spodoptera exigua*
ppm = part per million



The lead molecule was divided into three regions for SAR and optimization purposes: the benzhydrol head, the central piperidine scaffold, and the arylalkyl (benzyl) tail. We parallel processed all three simultaneously.

Synthesis

The BZP general synthesis is shown in the Scheme. For the synthesis of a variety of analogs in which the *benzhydrol* group was modified, ethyl

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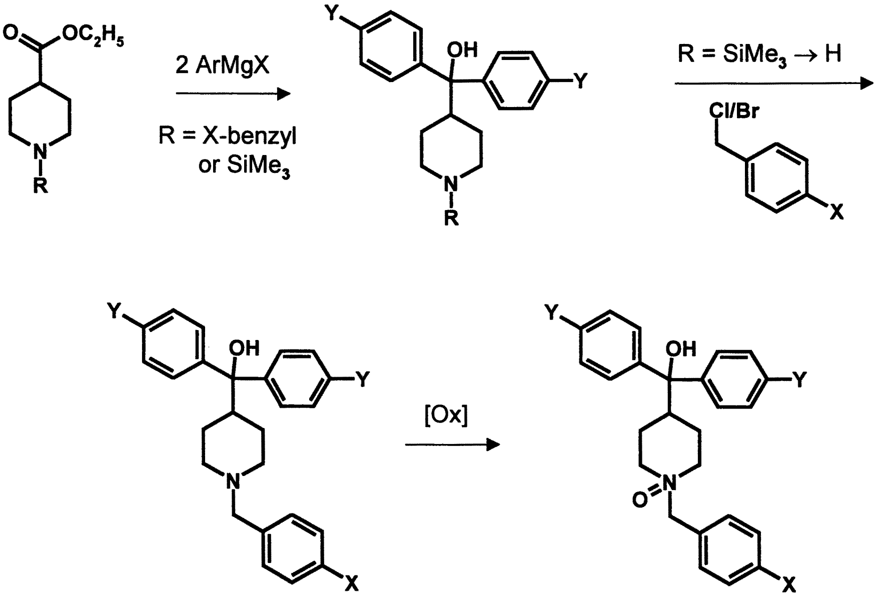
isonipecotate was benzylated with the benzyl halide of interest and the resulting ester reacted with two moles of an aryl or heteroaryl Grignard or lithium reagent. For sequential reactions with different organometallic reagents the first addition was performed on the corresponding Weinreb amide.

For synthesis of a variety of analogs in which the *benzyl* group was modified, the ethyl isonipecotate nitrogen was protected with a trimethylsilyl group. Addition of two moles of an aryl or heteroaryl organometallic reagent afforded the convergent benzhydrol intermediate which desilylated during aqueous work-up. Subsequent alkylation on nitrogen followed by optional N-oxidation with hydrogen peroxide or an organic peroxyacid provided the N-oxides.



Scheme. General Synthesis of BZP analogs

Optimization

The benzhydrol alcohol function, Z = OH, arose from the general synthesis method, from the double organometallic addition to the ester. A limited exploration of the SAR of Z revealed nothing superior to OH. The order of activity was: $Z = OH > Br > H \cong CN > F > SH \gg OCH_3, OC(=O)NHCH_3$. A general correlation with the steric property B_5, Sterimol maximum radius (*4*), seems apparent, with a steric optimum at Z = OH. In particular, sterically more demanding groups are much less active. This suggests an indirect steric role for Z in determining the orientation of the benzhydrol phenyl rings. Hydrogen bonding effects may also play a role. Isosteric replacement of heteroatoms for the benzhydrol carbinol moiety (C-Z: P=O or N) produced inactive analogs.

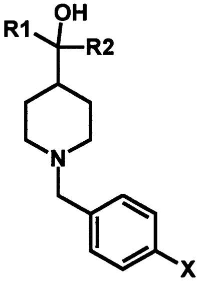
Focusing on the benzhydrol aromatic groups as R1 and R2 quickly demonstrated that at least one appropriately substituted aromatic or heteroaromatic group was required for activity; *both* R1 and R2 being aromatic or heteroaromatic provided the highest insecticidal potency.

One exception to the aromatic requirement for R1/R2 was found in a terminally fluorinated alkyl chain of appropriate length, Table II. An alkyl bridge of 4 methylenes with a terminal CF_3 group, ie., a 5-carbon chain, was the optimal aliphatic replacement for *p*-trifluoromethylphenyl or *p*-trifluoromethoxyphenyl, although this was still less active than the fluorinated aryl groups. It is interesting to note that the length of a phenyl group is the same as that of a butyl chain: Sterimol L of phenyl = 6.28Å; Sterimol L of butyl = 6.17Å. The phenyl and butyl groups are thus considered bridges to bring the CF_3 into binding space.

Table II. R1 = $(CH_2)_mCF_3$
R2 = *p*-$C_6H_4OCF_3$

m	*TBW Diet* *pI_{50}/pLC_{50}*
0	nm/nm
3	5.5/3.9
4	6.4/4.3
5	5.1/nm

nm = not measurable



Appropriate substitution on the benzhydrol aryl or heteroaryl rings was crucial. Unsubstituted phenyl provided nearly inactive analogs. The best activity was found with *para*-substitution of optimal size. Further substitution of the *para*-substituted aryl group reduced insecticidal potency. Heteroaromatic isosteres, e.g. pyridyl, also required appropriate substituents *para* to the point of attachment to the carbinol. These heteroaromatic groups were equivalent at best to their isosteric aryl groups and were much more difficult to synthesize.

Initially there seemed to be something unique about fluorinated Y substituents. The highest potency was observed with *p*-trifluoromethyl and *p*-

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trifluoromethoxy groups, yet *p*-fluoro was nearly inactive (as was unsubstituted phenyl). QSAR analysis helped us understand these apparently "unique" effects.

In a QSAR study of a set of symmetrically *para*-substituted (Y) analogs, TBW DIET weight inhibition was found to be parabolically related to π and linearly related to σ. No correlation with the steric parameter MR was observed. For the set studied π, σ and MR were found to be independent factors by factor analysis.

$$\text{TBW Diet pI}_{50} = 4.60 + 1.57\,\pi - 0.75\,\pi^2 + 1.55\,\sigma_{para}$$

$$n = 19, r = 0.932, s = 0.38, F = 33.11\ (0.00)$$
$$\pi\ \text{opt} = 1.05, \pi\ (CF_3) = 0.88, \pi\ (OCF_3) = 1.04$$

Thus, an electron-withdrawing group of optimum lipophilicity would express the highest activity. Note that the π value of the OCF_3 group is right at the calculated lipophilicity optimum. However, this equation tended to over predict certain substituents, especially those sterically larger than the training set. This led us to continue QSAR exploration with sterically more diverse subsets.

For the unsymmetrically substituted benzhydrols, with different *para*- and *para'*-substituents, various subsets were created, at first keeping Y = CF_3 or OCF_3 and varying Y'. It was clear from these initial small sets that there were several physicochemical properties, including sterics, determining insecticidal potency. In order to obtain enough analogs for a regression equation to support multiple parameters, we averaged the contributions of Y and Y', with the understanding that contributions to BZP binding would be an average of the enantiomers' physicochemical properties in the racemic mixtures which were tested. Thus, the π, σ, and MR values for Y and Y' were averaged and used as new parameters in a multiple linear regression analysis. This provided the regression equation shown with a positive contribution to TBW DIET weight inhibition by π, a positive contribution by σ, and a parabolic contribution by the steric property MR.

$$\text{TBW Diet pI}_{50} = 3.87 + 1.01\,\pi_{ave} + 0.80\,\sigma_{ave} + 2.49\,MR_{ave} - 1.58\,MR_{ave}^2$$

$$n = 29, r = 0.912, s = 0.35, F = 29.79\ (0.00)$$
$$MR_{ave}\ \text{opt} = 0.79, MR\ (CF_3) = 0.50, MR\ (OCF_3) = 0.79$$

Thus a relatively small, lipophilic, electronegative group of optimum size is required for best activity. This regression equation actually includes both

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unsymmetrical and symmetrical analogs. Note that the MR value of the OCF_3 group is right at the calculated steric optimum.

In order to examine the 3-D pharmacophore requirements, a benzhydrol CoMFA model, based on TBW DIET weight inhibition data was created (*5*). For the final model, $n = 35$, components = 2, s press = 0.52, $q^2 = 0.65$, $F = 10.6$ (0.0), steric contribution = 0.55; electrostatic contribution = 0.45. Most of the analogs contained at least one CF_3 or OCF_3, so the variation primarily appeared around a single benzhydrol aryl group. The steric model clearly showed unfavorable steric interactions scattered around one aryl group, and strong, favorable interactions near the *para* position. This suggests that there is an optimum length and width for the molecule. The electrostatic components of the model involve a number of positive regions as well as regions of negative contribution near the *para*-position of one phenyl ring. Interaction of the fluorines of the *para*-CF_3 or OCF_3 with the negative electrostatic region is clearly visible.

Conclusion

In conclusion, a symmetrically *para*-substituted benzhydrol group confers the highest insecticidal potency to the BZP chemistry class. This substitution pattern has synthesis and cost advantages over unsymmetrical analogs as well. The optimum *para* substituent is OCF_3, with CF_3 a close second. These results, presented in the Figure, are consistent with both 2-D and 3-D QSAR models.

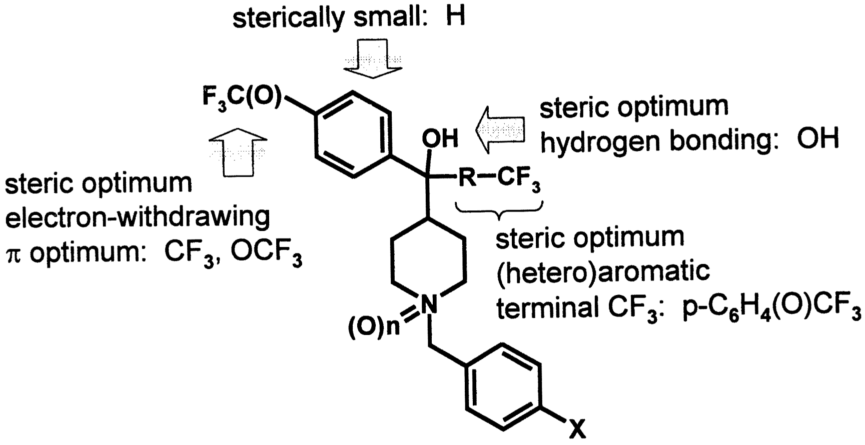

Figure. Benzhydrol SAR summary

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CF_3 and OCF_3 substituents combine the optimum lipophilic, steric, and electronic properties required for optimal interaction with the BZP biological target site, the voltage-sensitive sodium channel, site 9 (Soderlund's classification (*6*)), which is the same site as pyrazolines.

The final analogs are at least an order of magnitude more potent than the lead, although this is due primarily to the contribution of the benzyl substituent to the overall activity of the BZP molecule: propoxy vs. methoxy. The benzhydrol substitution in the lead molecule happened to be optimal in this case! Our final analogs are comparable in activity to cypermethrin in our biological assays, Table III.

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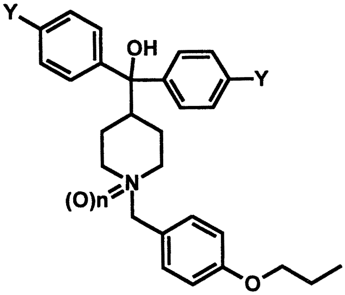

Table III. Most Potent Benzhydrol Analogs

Y	*n*	*TBW Diet* pI_{50}/pLC_{50}	*TBW Foliar* LC_{50} *ppm*	*BAW Foliar* LC_{50} *ppm*
CF_3	0	6.5/5.6	8.4	13
OCF_3	0	6.5/5.8	5.9	9.9
CF_3	1	6.5/5.9	11	17
OCF_3	1	6.6/6.1	5.2	3.8
Lead	0	6.1/4.6	59	81
CYP	-	7.3/6.5	3.9	6.9

CYP = cypermethrin

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Chapter 21

4-Nitroimino-1,3,5-oxadiazinanes: A New Type of Neonicotinoid Insecticides

P. Maienfisch[1], A. Rindlisbacher[1], H. Huerlimann[1], J. Haettenschwiler[1], A. K. Desai[2], V. S. Ekkundi[2], and V. D. Gangan[2]

[1]Research Chemistry, Optimisation, Syngenta Crop Protection AG, WRO–1060.1.14, CH–4002 Basel, Switzerland
[2]Hindustan Ciba-Geigy Ltd., Goregaon-Bombay, India

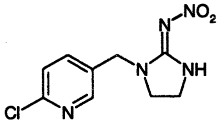
Our research on neonicotinoids has resulted in the discovery of insecticidally highly active 4-nitroimino-1,3,5-oxadiazinanes. A concise, practical synthesis of these compounds has been developed employing a Mannich type cyclization reaction of a monosubstituted nitroguanidine with formaldehyde in the presence of formic acid. Structure-activity relationships revealed that replacement of the nitroguanidine moiety by cyanoguanidine, urea or thiourea strongly decreased the insecticidal activity, while a methyl group as the pharmacophore substituent is clearly superior to a hydrogen atom, an acyl group or a C_2-C_4 alkyl group. Among these novel 4-nitroimino-1,3,5-oxadiazinanes, thiamethoxam was identified as the best compound and selected for worldwide development.

An important milestone in the history of modern insect control is marked by the discovery of the neonicotinoids (*1*). As the first representative, imidacloprid

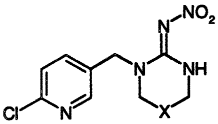
In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

1 (*2*) was introduced to the market in 1991 and since then, the neonicotinoids have become the fastest growing chemical class of insecticides. This tremendous success can be explained by their unique chemical and biological properties, such as broad-spectrum insecticidal activity, low application rates, excellent systemic characteristics, new mode of action (agonists of nicotinic acetylcholine receptors) and favorable safety profile.

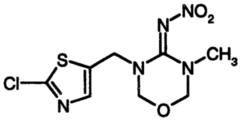
Ciba (since 1996: Novartis; now Syngenta) initiated a research program on neonicotinoids in 1985. At that time, little was known about the influence of the nitroimino heterocycle on the biological activity. We therefore prepared compounds **2**, **3** and **4**, possessing an additional heteroatom in the nitroimino heterocycle (*3*). The design of these compounds was directed by the hypothesis that the introduction of an additional heteroatom may lead to stronger binding to nicotinic acetylcholine receptors and/or improve the pharmocokinetic behavior. Bioassays revealed that among these compounds, the 4-nitroimino-1,3,5-oxadiazinane **3** possessed the highest insecticidal activity. Therefore, we initiated an optimization program to prepare a series of compounds **5** and to define the structure activity profile of this novel type of neonicotinoids.



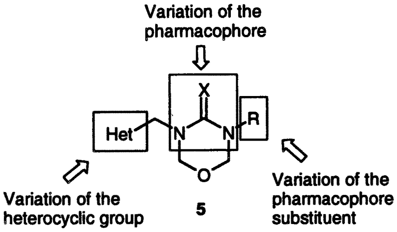
1
Imidacloprid



2 X = NCH_3
3 X = O
4 X = S



6
Thiamethoxam


Variation of the pharmacophore
X
Het
N
N
R
O
Variation of the heterocyclic group
5
Variation of the pharmacophore substituent

Our research resulted in the discovery of thiamethoxam **6**. This compound is the first commercially available second-generation neonicotinoid and belongs to the thianicotinyl subclass (*4-6*). It was first synthesized in 1991 and has been developed worldwide for use in more than 50 crops. After foliar, soil or seed treatment application, thiamethoxam provides excellent control of a broad range of commercially important pests, such as aphids, whiteflies, thrips, rice hoppers, Colorado potato beetle, flea beetles, wireworms, leaf miners as well as some lepidopterous species. Low use rates, flexible application methods, excellent efficacy, and the favorable safety profile make this new insecticide well suited for modern integrated pest management programs in many cropping systems.

Thiamethoxam is marketed since 1998 under the trademarks Actara® for foliar and soil treatment and Cruiser® for seed treatment.

Chemistry

At the start of our research, no practical synthetic route for the preparation of 4-nitroimino-1,3,5-oxadiazinanes was known. After some experimentation, we discovered a broadly applicable method for the synthesis of 3,5-disubstituted-4-nitroimino-1,3,5-oxadiazinanes (*3*). Thus, treatment of *S*-methyl-*N*-nitro-isothiourea (**7**) with amines **8** in ethanol at 50°C or 80°C afforded N-monosubstituted-N'-nitroguanidines **9**. Heating of compounds **9** in a 1:1 mixture of formaldehyde and formic acid for several hours to 80°C provided the 4-nitroimino-1,3,5-oxadiazinanes **10** in good to excellent yields. Replacement of formic acid by other acids such as acetic acid, trifluoroacetic acid and HCl resulted in a strong decrease of the yields. Compounds **10** could be coupled with heterocyclylmethyl chlorides **11** to afford the 4-nitroimino-1,3,5-oxadiazinanes **12**. Best yields for these alkylation reactions were obtained using 2.5 equivalents (eq.) of potassium carbonate as a base and dimethylformamide as solvent (Figure 1).

Variation of the pharmacophore substituent

The methodology described above (Figure 1) was successfully applied to the synthesis of a series of 2-chlorothiazol-5-ylmethyl substituted 4-nitroimino-1,3,5-oxadiazinanes **13** as illustrated in Table 1.

The preparation of 3-alkoxymethyl-5-(2-chlorothiazol-5-ylmethyl)-4-nitroimino-1,3,5-oxadiazinanes **16** was achieved as shown in Figure 2. Mannich type cyclization of nitroguanidine afforded 4-nitroimino-1,3,5-oxadiazinane (**14**), which could be selectively monoalkylated with the chloride **11a** (*7*). Under optimized reaction conditions (1.2 eq. **11a**, 1.0 eq. $KOC(CH_3)_3$, DMF-pyridine 4:1, -5°C to r.t.) and a special work-up procedure (crude dissolved in CH_2Cl_2, extracted with 2N NaOH, after acidification of the aqueous phase with HCl to pH = 4 the product separates as pale brown solid) compound **15** was obtained in 60% yield. Deprotonation of **15** with NaH in DMF followed by treatment with an alkoxymethyl chloride afforded the target compounds **16** in moderate to good yields (Table 2)

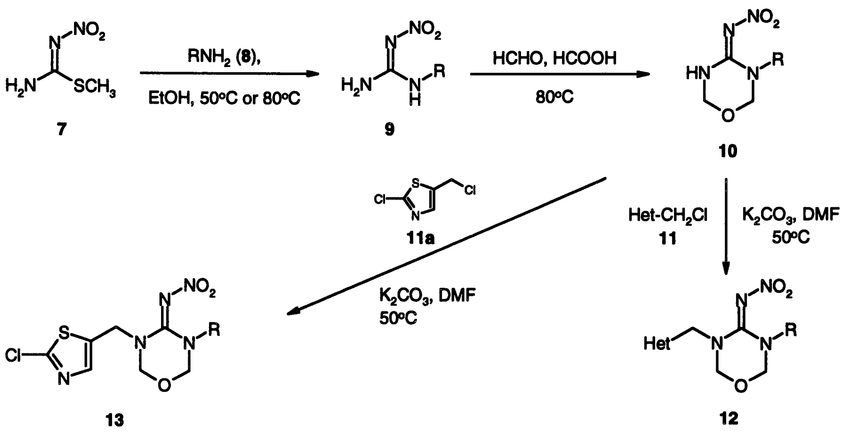

7
RNH2 (8),
EtOH, 50°C or 80°C
9
HCHO, HCOOH
80°C
10
11a
Het-CH2Cl
11
K2CO3, DMF
50°C
K2CO3, DMF
50°C
13
12

Figure 1. Preparation of 4-nitroimino-1,3,5-oxadiazinanes (R = alkyl, alkenyl, alkynyl, benzyl)

Table 1: Structure and chemical data of compounds 9, 10 and 13

R	*Compounds 9*		*Compounds 10*		*Compounds 13*	
	Yield [%]	*mp [°C]*	*Yield [%]*	*mp [°C]*	*Yield [%]*	*Mp [°C]*
CH_3	97	160-162	71	140-142	71	140-141
CH_3CH_2	87	146-148	87	96-97	73	110-112
$CH_3CH_2CH_2$	78	98-99	85	79-80	68	80-82
$(CH_3)_2CH$	95	155-157	54	101-103	44	126-128
$CH_3CH_2CH_2CH_2$	65	74-76	82	86-87	47	71-73
$HC{\equiv}C\text{-}CH_2$	67	176-177	42	99-100	44	176-177
$CH_3OCH_2CH_2$	87	120-122	81	95-96	61	amorphous
$C_6H_5\text{-}CH_2$	87	183-185	88	104-105	72	104-106
$4\text{-}Cl\text{-}C_6H_4\text{-}CH_2$	93	194-195	86	140-141	65	106-108

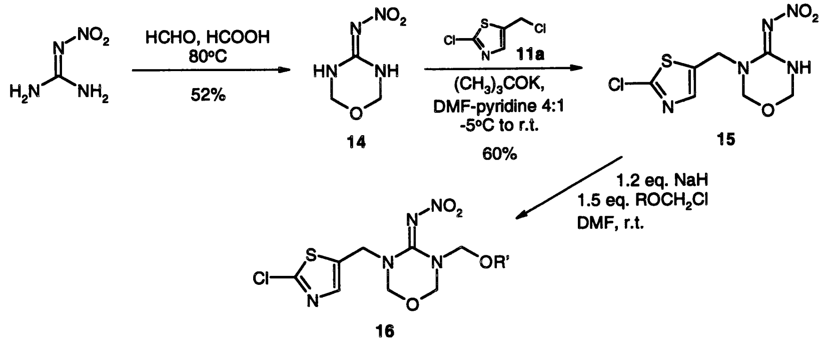


Figure 2. Preparation of 3-alkoxymethyl-derivatives 16

Table 2: Structure and chemical data of compounds 16

R'	*Compounds 16*	
	Yield [%]	*mp [°C]*
CH_3	45	102-104
$(CH_3)_2CH$	44	amorphous
$CH_3CH_2CH_2CH_2$	61	amorphous
$H_2C{=}CH{-}CH_2$	48	amorphous
$HC{\equiv}C{-}CH_2$	36	amorphous
$C_6H_5{-}CH_2$	11	amorphous
$4{-}Cl{-}C_6H_4$	36	135-145

Acylated derivatives **17**, **18**, **19** and **20** were prepared as shown in Figure 3. Compound **15** was first treated at 5-10°C with 1.2 eq. of NaH in anhydrous DMF and pyridine, then 2.5-3.0 eq. of an acid chloride, a chloro formate or a chloro oxoacetate were added and the reaction was stirred for 3-5 h at room temperature (r.t.) to afford compounds **17**, **18** and **20** in moderate yields (Table 3). In the case of isocyanates as coupling reagents, the reaction did not occur at r.t. but needed heating to 70-80°C for 5 to 6 hours. Compound **19** could only be obtained in low yields from **15** and phenyl isocyanate (Figure 3).

Variation of the pharmacophore

Some variations of the pharmacophore (N-C(N)=X) have been performed. The cyanoimino derivative **23** was prepared starting from N-methyl-N'-

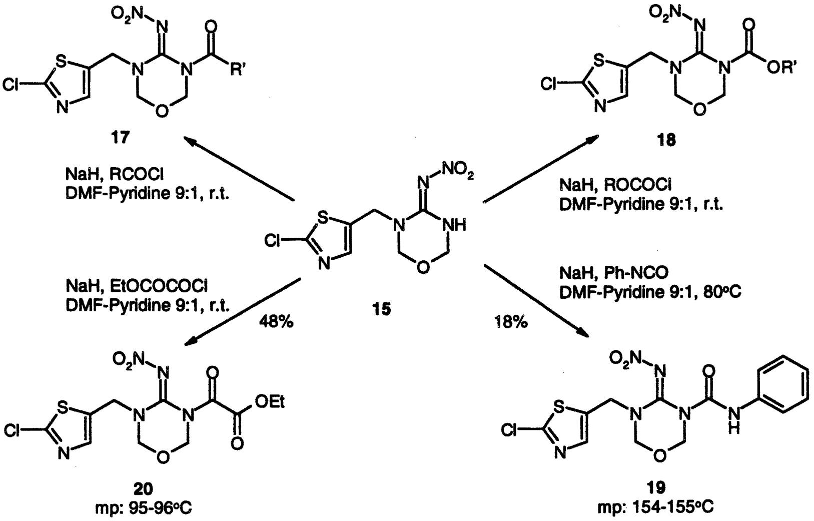

17
NaH, RCOCl
DMF-Pyridine 9:1, r.t.
18
NaH, ROCOCl
DMF-Pyridine 9:1, r.t.
15
NaH, EtOCOCOCl
DMF-Pyridine 9:1, r.t.
48%
NaH, Ph-NCO
DMF-Pyridine 9:1, 80°C
18%
20
mp: 95-96°C
19
mp: 154-155°C

Figure 3. Preparation of 3-acyl-derivatives 17, 18, 19 and 20

Table 3: Structure and chemical data of compounds 17 and 18

R'	*Compounds 17*		*Compounds 18*	
	Yield [%]	*mp [°C]*	*Yield [%]*	*mp [°C]*
CH_3	29	124-125	8	125-126
CH_3CH_2	51	152-153	42	amorphous
$(CH_3)_2CH$	36	158-159	-	-
$CH_3CH_2CH_2CH_2$	36	158-159	51	amorphous
$(CH_3)_3C$	22	144-145	38	138-139
C_6H_5	5	148-149	-	-

cyanoguanidine **21**, which was obtained in 56% from sodium dicyanamide and methylamine. The conversion of **21** to 3-methyl-4-cyanoimino-1,3,5-oxadiazinane (**22**) was not achieved under the reaction conditions applied for the preparation of the 4-nitroimino-1,3,5-oxadiazinanes **10**. However, treatment of **21** with a large excess of aqueous formaldehyde at pH 8 gave compound **22** in moderate yield. Alkylation of **22** with the chloride **11a** afforded the cyanoimino-analogue **23**.

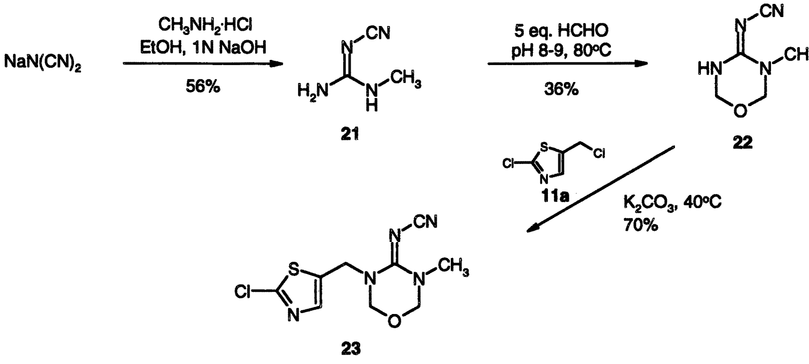

NaN(CN)₂
CH₃NH₂·HCl
EtOH, 1N NaOH
56%
21
5 eq. HCHO
pH 8-9, 80°C
36%
22
11a
K₂CO₃, 40°C
70%
23

Figure 4. Preparation of the 4-cyanoimino-1,3,5-oxadiazinane 23

The urea **24** and the thiourea **25** were prepared starting from thiamethoxam **6**. Treatment of **6** with 1 equivalent of potassium hydroxide in tert. butanol provided the urea **24**, which was reacted with Lawesson's reagent to yield the thiourea **25** in 13% yield. Replacement of Lawesson's reagent by phosphorus pentasulfide resulted in much better yields in the sulfuration reaction.

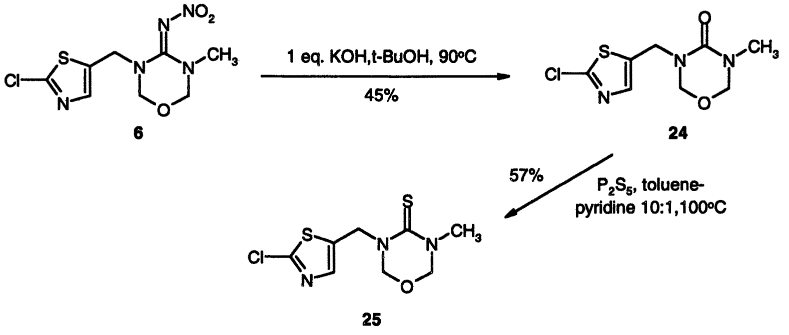

6
1 eq. KOH,t-BuOH, 90°C
45%
24
57%
P₂S₅, toluene-
pyridine 10:1,100°C
25

Figure 5. Preparation of urea 24 and thiourea 25

Biology

Approximately two hundred compounds were prepared by the synthetic procedures described in the preceding section. The compounds were tested in our primary screening at 100, 50 and 12 ppm against *Diabrotica balteata* (*D.b.*) and *Aphis craccivora* (*A.c.*) for contact/feeding activity and at 12 ppm against *Myzus persicae* (*M.p.*) for systemic activity:

Diabrotica balteata (contact/feeding activity): Maize seedlings are placed on filter paper in plastic cups, and 3 ml of the test solutions are pipetted onto them. In addition, seedlings were treated in a spray chamber and infested with 12-15 2nd instar (L_2) larvae of *D.b.* (banded cucumber beetle). The samples are checked for mortality 6 days after treatment.

Aphis craccivora (contact/feeding activity): Pea seedlings, infested with an *A.c.* (black bean aphid) population of mixed ages, are treated with the test solutions in a spray chamber and checked for mortality 6 days after treatment.

Myzus persicae (systemic activity): Pea seedlings, infested with a *M.p.* (green peach aphid) population of mixed ages, were placed directly in the test solutions and assessed for mortality 6 days after introduction.

The biological results are shown in Tables 4 and 5. The activity against *D.b.* and *A.c.* is reported as A (80-100% mortality at 12 ppm), B (80-100% mortality at 50 ppm), C (80-100% mortality at 100 ppm) and D (<80% mortality at 100 ppm) and for *M.p.* as A (80-100% mortality at 12 ppm) and D (<80% mortality at 12 ppm).

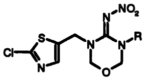
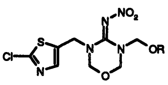
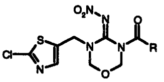
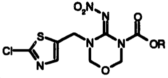
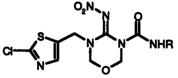
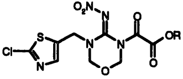
Structure-Activity Relationships

This section will focus on the insecticidal activity of representative examples of 4-nitroimino-1,3,5-oxadiazinanes in order to illustrate the structure-activity relationships demonstrated by these compounds.

Effect of Pharmacophore Substituent

A wide range of modifications of the pharmacophore substituent R (R = hydrogen, alkyl, alkenyl, alkynyl, alkoxymethyl, alkenyloxymethyl, alkynyloxymethyl, phenoxymethyl, benzyl, alkylcarbonyl, benzoyl and alkoxycarbonyl) led to compounds providing moderate to good insecticidal

Table 4: Variation of the pharmacophore substituent

Structure	*Comp.*	*R*	*D.b.*	*A.c.*	*M.p*
	**15**	H	A	B	A
	6	CH_3	A	A	A
	13a	CH_3CH_2	A	C	A
	13b	$CH_3CH_2CH_2$	B	D	A
	13c	$(CH_3)_2CH$	D	D	D
	13d	$CH_3CH_2CH_2CH_2$	D	D	n.t.
	13e	$HC\equiv C-CH_2$	A	D	n.t.
	13f	$CH_3OCH_2CH_2$	D	D	n.t.
	13g	$C_6H_5-CH_2$	B	D	A
	13h	$4-Cl-C_6H_4-CH_2$	C	D	D
	**16a**	CH_3	A	D	A
	16b	$(CH_3)_2CH$	A	D	A
	16c	$CH_3CH_2CH_2CH_2$	A	C	D
	16d	$H_2C=CH-CH_2$	B	B	A
	16e	$HC\equiv C-CH_2$	A	B	A
	16f	$CH_3OCH_2CH_2$	D	D	D
	16g	$C_6H_4CH_2$	A	D	A
	16h	$4-Cl-C_6H_4$	B	D	D
	**17a**	H	D	D	D
	17b	CH_3	A	D	A
	17c	CH_3CH_2	A	B	A
	17d	$(CH_3)_2CH$	A	D	A
	17e	$(CH_3)_3C$	C	D	A
	17f	C_6H_5	A	D	A
	**18a**	CH_3	A	D	A
	18b	$(CH_3)_3C$	A	D	A
	**19**	C_6H_5	D	D	A
	**20**	CH_3CH_2	D	D	D

activity (Table 4). Steric as well as electronic factors seem to have an important influence on the biological activity. The most potent compounds are the unsubstituted compound **15**, its methyl analog **6**, the propargyloxymethyl derivative **16e** and the ethylcarbonyl derivative **17c**. Among these compounds, only **6** (thiamethoxam) was found to be active at 12 ppm in all three test systems.

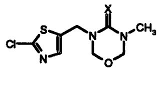
When Y is an alkyl group, the activity decreases with the chain length and the steric bulk (Me > Et > n-Pr >> i-Pr, n-Bu). Somewhat surprisingly, the methyl-substituted compound **6** is clearly more active than the unsubstituted compound **15**. This is in contrast to the imidacloprid series where the activity drops significantly when a methyl group is introduced as the pharmocophore substituent (data not shown).

Most compounds **17** and **18** possess good activity against D.b. and M.p. but are weak against A.c. In this series, steric factors seem to be less important for biological activity.

Effect of Pharmacophore

The insecticidal activity is highly dependent on the pharmacophore (N-C(N)=X) as is shown in Table 5. Among the compounds tested, best activity was observed for the nitroimino compound **6** (X = $N-NO_2$). Replacement of the nitroimino group by a cyanoimino moiety (compound **23**) clearly diminished the activity, while compounds like the urea **24** (X = O), the thiourea **25** (X = S) and the guanidine **26** (X = NH) were not active at 100 ppm. These differences in the biological activities seem to be clearly related to the electronic properties of the pharmacophore moiety. Activity is only found if the functional group X is strongly electron-withdrawing and has a hydrogen-bond accepting head like in $N-NO_2$ and in N-CN.

Table 5: Variation of the pharmacophore

Structure	*Comp.*	*X*	*D.b.*	*A.c.*	*M.p*
	**6**	$N-NO_2$	A	A	A
	23	N-CN	B	B	A
	26	NH	D	D	D
	24	O	D	D	D
	25	S	D	D	D

General Structure-Activity Relationships

Using the biological data generated in this study together with the results from a series of further 4-nitroimino-1,3,5-oxadiazinanes and related compounds, a general structure-activity relationship emerged and is represented in Figure 6.

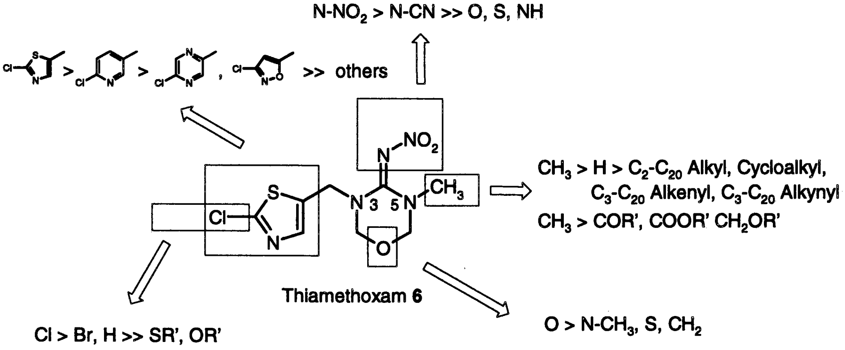


Figure 6. General structure-activity profile for 4-nitroimino-1,3,5-oxadiazinanes

Conclusions

In the present work, the synthesis and insecticidal activity of a series of novel 4-nitroimino-1,3,5-oxadiazinanes are described. The structure-activity profile of these compounds demonstrated the rather limited variability of the pharmacophore N-C(N)=X. Activity was only found if the functional group X is strongly electron-withdrawing and has a hydrogen accepting head like N-NO_2 and N-CN. As pharmacophore substituent, a methyl group is clearly superior to a hydrogen group, an acyl group or a C_2-C_4 alkyl group.

Our research on 4-nitroimino-1,3,5-oxadiazinanes has resulted in the discovery of thiamethoxam. This compound has broad-spectrum insecticidal activity and offers excellent control of a wide variety of commercially important pests in most crops. Thiamethoxam has been marketed since 1998 under the trademarks Actara® for foliar and soil treatment and Cruiser® for seed treatment.

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Chapter 22

Improved Preparation of Sap Beetle (Coleoptera: Nitidulidae) Aggregation Pheromones

Richard J. Petroski and David Weisleder

National Center for Agricultural Utilization Research, Agricultural Research Service, REE, U.S. Department of Agriculture, 1815 North University Street, Peoria, IL 61604

Sap beetles, belonging to the genus *Carpophilus*, produce aggregation pheromone blends that are composed of conjugated triene and tetraene hydrocarbons having all *E*-double-bond configuration. The preparation of (2*E*,4*E*,6*E*,8*E*)-3,5,7-trimethyl-2,4,6,8-decatetraene (**1**) and (3*E*,5*E*,7*E*,9*E*)-6,8-diethyl-4-methyl-3,5,7,9-dodecatetraene (**2**) was improved in terms of overall yield: 46% vs 40% for compound **1** and 20% vs 8% for compound **2**. A mild Horner-Wadsworth-Emmons olefination of a starting aldehyde was used to build up the carbon chain, two carbons at a time with either methyl or ethyl branches. The disubstituted double bond containing the terminal methyl group was added with a Wittig reaction in the case of compound **1** but a new *E*-double-bond selective alkylidenation sequence, that allows much better stereochemical control than the Wittig reaction, was used in the construction of compound **2**. The alkylidenation sequence consists of four steps. Horner-Wadsworth-Emmons olefination of an aldehyde with triethylphosphonoacetate yields an α,β-unsaturated ester with > 99% *E*-double-bond configuration. Reduction of the unsaturated ester with lithium aluminum hydride affords an allylic alcohol.

U.S. government work. Published 2002 American Chemical Society

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

The allylic alcohol is acetylated under mild conditions with acetic anhydride, triethylamine and 4-dimethylaminopyridine (DMAP) as the acylation catalyst. Displacement of the acetate function with a methyl group is accomplished with a methylmagnesium chloride Grignard reagent in the presence of lithium tetrachlorocuprate as the carbon-carbon cross coupling catalyst. The overall yield for the alkylidenation sequence was 41%, but > 99% *E*-double-bond configuration was obtained.

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Sap beetles, belonging to the genus *Carpophilus*, are pests in a wide variety of agricultural products. Aggregation pheromones have been identified for nine species of sap beetles; the chemistry and biology has been reviewed (*1*). The pheromones are composed of alkyl-branched, conjugated triene or tetraene hydrocarbons having all *E*-double-bond configuration. These pheromones have potential uses as pest management tools.

A project was undertaken to improve the synthetic pathway leading to the sap beetle pheromones (*2*). Two compounds were selected as synthetic targets: (2*E*,4*E*,6*E*,8*E*)-3,5,7-trimethyl-2,4,6,8-decatetraene (**1**) and (3*E*,5*E*,7*E*,9*E*)-6,8-diethyl-4-methyl-3,5,7,9-dodecatetraene (**2**). Compound **1** is the major component of the aggregation pheromone of the driedfruit beetle, *Carpophilus hemipterus* (L.) (*3*) and compound **2** is the aggregation pheromone of the corn sap beetle, *Carpophilus dimidiatus* (F.) (*4*) as well as for a related species, *Carpophilus antiquus* Melsheimer (*5*).

Compounds **1** and **2** were previously prepared in overall yields of 40% and 8%, respectively (*2*, *5*). Compound **2** has been prepared only as a mixture of 9*E*- and 9*Z*-double-bond isomers (70% *E*) by using a Wittig reaction to add the disubstituted double bond and terminal ethyl group (*5*). Recent synthetic improvements are reported in this paper.

Experimental Details and Discussion

Compound **1** was prepared as outlined in Figure 1. Tiglic aldehyde, (2*E*)-2-methyl-2-butenal, was readily converted to the 2*E*,4*E*-conjugated ester **3** using an improved Horner Wadsworth Emmons (HWE) olefination reaction utilizing triethyl-2-phosphonopropionate (TEPP) as the phosphonate, lithium *tert*-butoxide as the base and hexane as the reaction solvent (*6*). High *E*-isomer selectivity (e.g. > 98% for compound **3**) and fewer side products (evidenced by GC analysis of crude products) were observed using this milder HWE procedure. The ester **3** was reduced to the conjugated allylic alcohol **4** with $LiAlH_4$, and mild partial oxidation

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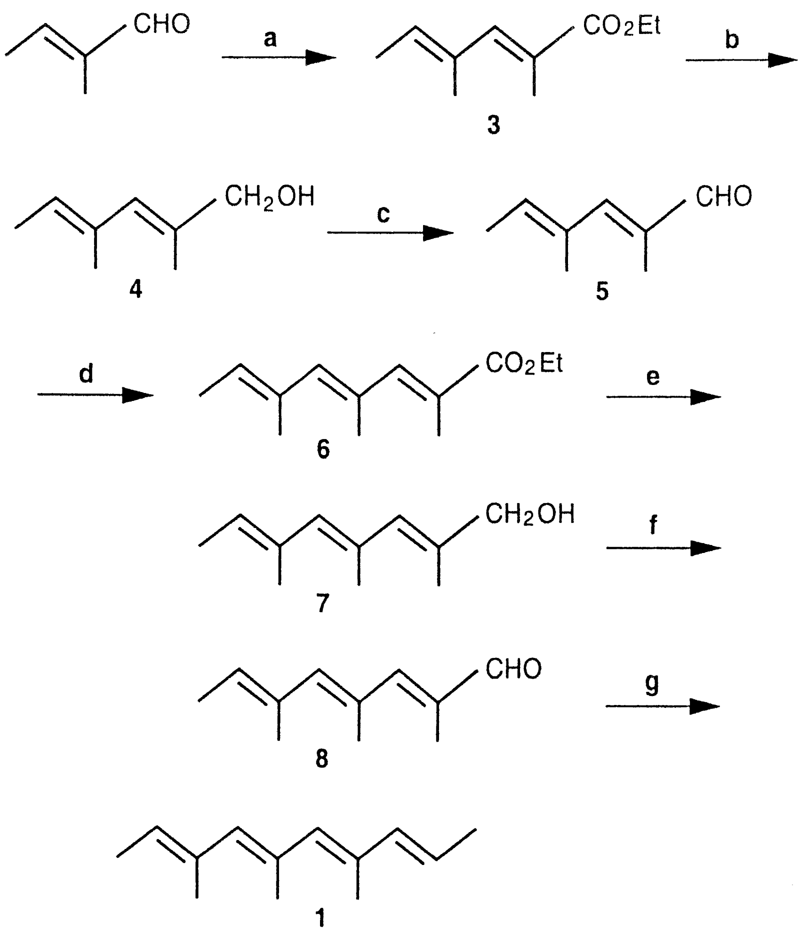

Figure 1. Preparation of Compound 1: (a) TEPP, LiOtBu, hexane, 25 °C, 1 h (95% yield); (b) $LiAlH_4$, Et_2O, 0 °C (80% yield); (c) MnO_2, CH_2Cl_2, 25 °C, 48 h, (90% yield); (d) TEPP, LiOtBu, hexane, 25 °C, 1 h (97% yield); (e) $LiAlH_4$, Et_2O, 0 °C (88% yield); (f) MnO_2, CH_2Cl_2, 25 °C, 72 h, (94% yield); (g) $[Ph_3PCH_2CH_3]^+Br^-$, n-BuLi, THF, 0 °C (84% yield). Reported yields are isolated yields. The overall yield of compound 1 from (2E)-2-methyl-2-butenal was 46%.

with MnO_2 in CH_2Cl_2 afforded the aldehyde **5**. This three step process was repeated to prepare compounds **6**, **7**, and **8**, respectively. The milder reaction sequence facilitates the synthetic pathway leading to **8**. Conversion of **8** to **1** has been reported previously (*2*). The final Wittig coupling reaction was used to create the disubstituted double bond containing the terminal methyl group (*2*). Acceptable stereoselectivity (*E*/*Z* disubstituted-double-bond isomer ratio of 8/1 to 10/1) was observed (*2*) and the technical grade material could be used in field studies (*3*). The overall yield of compound **1** from tiglic aldehyde was 46% using the improved synthetic pathway; stereochemical purity at the trisubstituted double bond positions was only slightly improved (< 2% total *Z*-isomers). The previously reported overall yield of compound **1** from tiglic aldehyde was 40% (*2*).

Compound **2** was prepared as outlined in Figure 2. Compound **9** was readily prepared from (2*E*)-2-methyl-2-pentenal with triethyl-2-phosphonobutyrate (TEPB) as the phosphonate in the improved HWE reaction (*6*). The ester **9** was reduced to the conjugated allylic alcohol **10** with $LiAlH_4$, and mild partial oxidation with MnO_2 in CH_2Cl_2 afforded the aldehyde **11**. This three step process was again repeated to prepare compounds **12**, **13**, and **14**, respectively. The overall yield of compound **14** from 2-methyl-2-pentenal was 49%. At this point, a synthetic sequence to increase the 70% *E*- / 30% *Z*-isomer ratio at the disubstituted double bond in compound **2** was sought.

The new alkylidenation sequence which follows results in exclusively *E*-stereochemistry about the disubstituted double bond in compound **2**. Compound **15** was prepared from compound **14** by using triethylphosphonoacetate (TEPA) as the phosphonate, but utilizing the same procedure as with triethyl-2-phosphonopropionate in the HWE reaction (*6*). The ester **15** was reduced to the conjugated allylic alcohol **16** with $LiAlH_4$. The allylic alcohol **16** was acetylated with acetic anhydride, triethylamine and 4-dimethylaminopyridine (DMAP) as the acylation catalyst (*7,8*). Conversion of the allylic acetate **17** to the pheromone **2** was accomplished by cross coupling with a methyl Grignard reagent in the presence of Li_2CuCl_4; a procedure previously used to prepare natural products (*9,10*). The overall yield for the alkylidenation sequence (**14** to **17**) was 41%, but the *E*-selectivity about the disubstituted double bond in compound **2** was improved from 70% to > 99%. Compound **2** was prepared in 20% overall yield from 2-methyl-2-pentenal; the previously reported overall yield from the same starting aldehyde was only 8%, with 70% *E*-selectivity about the disubstituted double bond (*5*).

A bridged tetrahydrophosphole ylide has been used in *E*-selective (80% -90%) Wittig reactions (*11*), but the preparation of the ylide for ethylidenation is, itself, a multistep synthesis. The ethylidenation sequence reported herein requires four steps, and utilizes commercially available reagents or catalysts.

Synthetic ester products **3**, **6**, **9** and **12** were purified by Kugelrohr distillation. Synthetic alcohol and aldehyde products could be used directly, without kugelrohr

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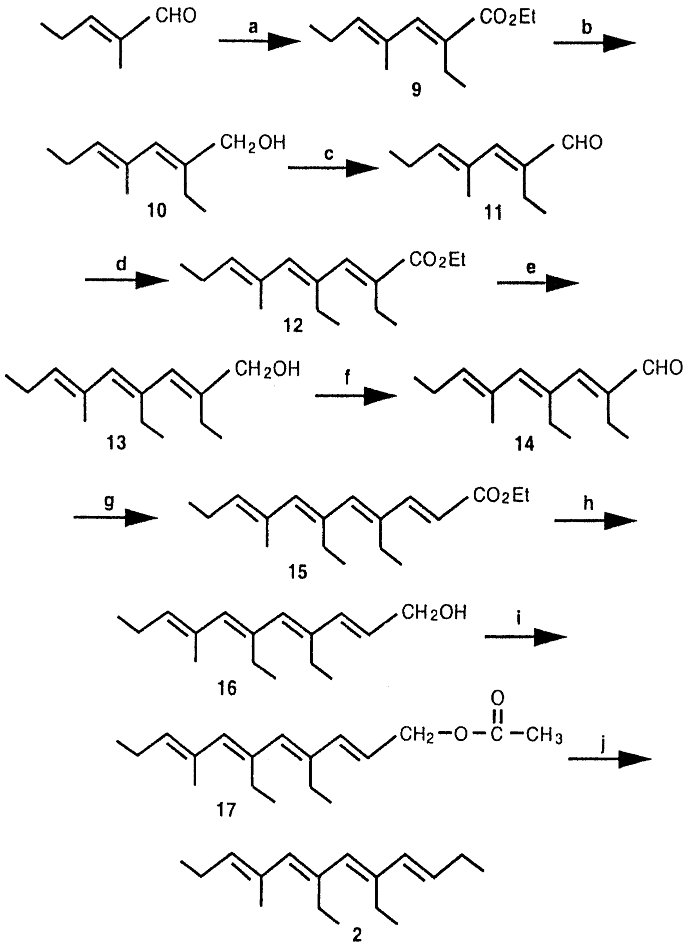
CHO
a
CO2Et
b
9
CH2OH
c
CHO
10
11
d
CO2Et
e
12
CH2OH
f
CHO
13
14
g
CO2Et
h
15
CH2OH
i
16
O
CH2–O–C–CH3
j
17
2

Figure 2. Preparation of Compound 2: (a) TEPB, LiOtBu, hexane, 25 °C, 4 h (92% yield); (b) $LiAlH_4$, Et_2O, 0 °C (90% yield); (c) MnO_2, CH_2Cl_2, 25 °C, 72 h, (84% yield); (d) TEPB, LiOtBu, hexane, 25 °C, 4 h (78% yield); (e) $LiAlH_4$, Et_2O, 0 °C (94% yield); (f) MnO_2, CH_2Cl_2, 25 °C, 72 h, (96% yield); (g) TEPA, LiOtBu, hexane, 25 °C, 1 h (80% yield); (h) $LiAlH_4$, Et_2O, 0 °C (82% yield); (i) Ac_2O, Et_3N, DMAP, 25 °C, 14 h (90% yield); (j) CH_3MgCl (3 eq.), Li_2CuCl_4, THF, -10 °C, 3 h (70% yield). Reported yields are isolated yields. The overall yield of compound 2 from (2E)-2-methyl-2-pentenal was 20%.

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distillation, in subsequent reactions (*2*). Some unwanted *Z*-isomer (< 2% for compounds **3** or **6** and < 15% for compounds **9** or **12**) was formed during each HWE olefination (evidenced by shorter GC retentions but almost identical mass spectra, compared with the *E*-isomer). The proportion of unwanted *Z*-isomer decreased during the subsequent reduction and partial oxidation steps because the reaction conditions caused some isomerization of *Z*-double bonds to the thermodynamically more stable *E*-configuration (*2*). The level of unwanted *Z*-isomers at any of the trisubstituted double bond positions was reduced to only about 3% in the final pheromone products such as compound **1** (*2*). The major impurity was always the *Z*-isomer at the disubstituted double bond resulting from the Wittig reaction (*2*). The *Z*-isomer at the disubstituted double bond is completely absent when the new alkylidenation sequence is used.

Unfortunately, even mild Kugelrohr distillation of conjugated tetraene ester **15** resulted in some (5% to 10%) product degradation. We also found that conjugated tetraene aldehydes and hydrocarbons seemed to be more sensitive to heat or traces of acid than conjugated tetraene esters, alcohols, or acetates. The tetraene hydrocarbons **1** and **2** could be safely stored in hexane (50 mg/ mL) at -20° C or less.

The new synthetic pathways to the sap beetle pheromones, described in this paper, employs milder reaction conditions (e.g. lithium *tert*-butoxide base vs *n*-butyllithium base) to synthesize most of the carbon chain and a new alkylidenation sequence to improve the *E*-stereochemistry of the disubstituted double bond in the case of *Carpophilus dimidiatus* aggregation pheromone, compound **2**, where stereochemical control has been shown to be difficult.

Acknowledgments

We thank Bruce W. Zilkowski for acquiring mass spectral data and Dr. Robert J. Bartelt for helpful discussions.

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*Telephone (309) 681-6222; Fax (309) 681-6693; Email: petrosrj@ncaur.usda.gov.
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Chapter 23

Using Classic and Quantum Parameters to Determine Monoterpenoids' Insecticidal Quantitative Structure–Activity Relationships

Justin A. Grodnitzky and Joel R. Coats

Department of Entomology, Iowa State University, Ames. IA 50011

Monoterpenoids are naturally occurring plant compounds that have been shown to have toxicity to insects. Quantitative structure-activity relationships (QSAR)s were developed for monoterpenoids and their derivatives. Monoterpenoid phenols and alcohols (thymol, carvacrol, carveol, and geraniol) and their ester derivatives were examined to determine the structural features of the molecules that are essential for their toxicity to house flies. Using a variety of classical and quantum parameters, we found that electronic properties within each monoterpenoid group showed a high correlation with house fly toxicity.

Monoterpenoids are naturally occurring plant compounds that are found in higher-order plants. These compounds are secondary metabolites; they are usually synthesized from two isoprene units, and are therefore 10-carbon molecules. Biosyntheses of monoterpenoids are accomplished via the mevalonic acid pathway. Monoterpenoids are further processed by the plant through various oxidation steps. These compounds seem to play no major role in the metabolic functioning of the plants, and their role is thought to be less critical (secondary). There are several functions for monoterpenoids in the plant. One

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ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

function is to aid in pollination of the plant by attracting certain insects to the plant. Another function of monoterpenoids is to defend against plant pathogens, herbivores, or competing plant species.

Plants and insects have co-evolved for millions of years. Plants have developed the capability to produce secondary metabolites in order to protect themselves against different types of pathogens and herbivores. The pathogens include fungi and bacteria, and the herbivores include insects, birds, mammals, etc. Secondary metabolites, such as monoterpenoids, are potentially good naturally occurring insecticides because of the co-evolution through which they were developed. Some monoterpenoids have shown insecticidal activity, and a few of these compounds are used as commercial pesticides (*d*-limonene, menthol, citronellal, and linalool) *(1)*. Although, these monoterpenoids are being used commercially, the mode of action is still unknown. In addition, no quantitative structure-activity relationships (QSARs) have been determined up to this point.

We examined four monoterpenoids (phenols and alcohols) and their ester analogs. We tested linear monoterpenoids (geraniol), cyclic monoterpenoids (carveol), and aromatic monoterpenoids (carvacrol, thymol) to find a relationship between all the monoterpenoids and their toxicity. By using toxicity to house flies, we tried to correlate toxicity with various classical and quantum parameters. Specific parameters were chosen in order to help explain toxicity. These parameters were chosen to represent the features of molecules that are important in receptor-ligand interaction. Size and shape of a molecule is extremely important for receptor-ligand interactions. If the receptor does not accommodate the molecule because of its size or shape, then the molecule cannot generate its effect on the system. In our case, its effect would be toxicity to house flies. To discern if shape and size of the monoterpenoids are important for their toxicity, we examined several classical parameters. These independent variables are molecular connectivity indices (0,1,2), valance connectivity indices (0,1,2), shape indices (1,2,3), and molar refractivity.

The other important criterion that must be met for receptor-ligand interactions to occur is the adherence of the ligand to the receptor. Molecular interactions can be explained by affinity due to electrostatic interactions, London dispersion forces, and hydrophobic interactions. We examined classical and quantum parameters to help explain these interactions. Log P and molar refractivity are the classical parameters chosen to represent hydrophobic interactions and London dispersion forces *(2)*. The quantum parameters were chosen to represent both electrostatic interactions and London dispersion forces. Highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), dipole moment, polarizability, and Mulliken population are the quantum parameters chosen to represent receptor-ligand interaction, which can ultimately cause mortality to house flies.

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Synthesis of monoterpenoid esters

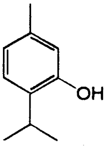
Monoterpenoid parent alcohols or phenols, carveol, geraniol, thymol, and carvacrol, (1 mole) were added to their corresponding anhydride or acid chloride (2 moles) to form ester derivatives in the presence of a catalytic amount of pyridine (2-5 drops). Methylene chloride was used as the solvent, and the reaction was allowed to stir for 24-48 hr at room temperature. The reactions were monitored by thin-layer chromatography using a 9:1 hexane:acetone mobile phase and developed by vanillin spray (8g vanillin, 1.25ml sulfuric acid brought up to 250ml with methanol). The reaction was worked up with four ($NaHCO_3$ and water) washes. Methylene chloride was removed using a rotary evaporator. Compounds were purified using silica gel-column clean up, using a 19:1 hexane:acetone solvent system. Identities of the esters were determined using TLC, comparing Rf values of the parent alcohols or phenols against reaction products. Identities were confirmed using ^{1}H-NMR 300 Mhz. A total of 25 monoterpenoids were used in this study, which includes the four parent molecules and 21 esters (Fig. 1) (Fig. 2). Four geranyl esters were made from geraniol, and five esters were made from each of the remaining monoterpenoids (thymol, carvacrol, and carveol).

House fly toxicity testing

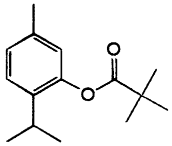
LD_{50} values were obtained for all 25 monoterpenoids. Topical application was used to apply 1 µL of various concentrations of monoterpenoid to the pronotum of *Musca domestica* (house fly). We placed 10 treated house flies in a jar and for each concentration, three replications of monoterpenoid were used. At the end of the 24-hr exposure, mortalities of the house flies were recorded. LD_{50}s of all the monoterpenoids were calculated using the Spearman-Karber method *(3)*. LD_{50} values are shown (Fig 1) (Fig 2). Some compounds' LD_{50} values were previously report from our lab *(4)*.

These showed a range of toxicity to house flies, ranging from LD_{50} of 0.17 µmol/fly to 2.35 µmol/fly. The two monoterpenoids which have the greatest toxicity are geranyl chloroacetate with a LD_{50} value of 0.17 µmol/fly and thymol with a LD_{50} value of 0.22 µmol/fly. There is no obvious structural reason why these two compounds have the most insecticidal activity. Geranyl chloroacetate is a derivative of an acyclic monoterpenoid, and thymol is an aromatic monoterpenoid. In the thymol group, thymol was more toxic than its derivatives; however; in the geraniol group, all the derivatives were more toxic than geraniol. Also for the carveol group, carveol was one of the least toxic compounds within that group. Carvacrol, on the other hand, was one of the

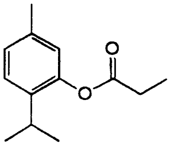
Thymol Compounds:



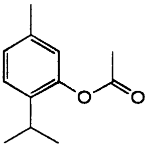
Thymol
LD_{50}=0.22 (0.20-0.24)



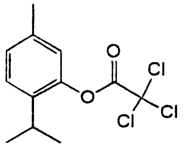
Thymyl pivalate
LD_{50}=0.34 (0.22-0.42)



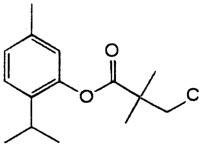
Thymyl propionate
LD_{50}=0.49 (0.40-0.62)



Thymyl acetate
LD_{50}=0.49 (0.44-0.54)

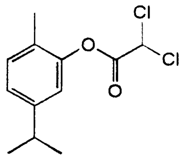


Thymyl trichloroacetate
LD_{50}=0.62 (0.56-0.69)

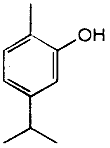


Thymyl chloropivalate
LD_{50}=1.12 (0..98-1.27)

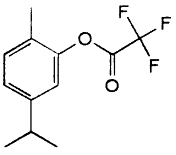
Carvacrol Compounds:



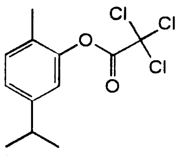
Carvacryl dichloroacetate
LD_{50}=0.39 (0.41-0.53)



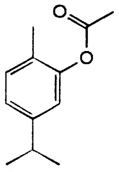
Carvacrol
LD_{50}=0.42 (0.40-0.43)



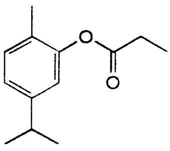
Carvacryl trifluoroacetate
LD_{50}=0.46 (0.41-0.53)



Carvacryl trichloroacetate
LD_{50}=0.47 (0.43-0.51)



Carvacryl acetate
LD_{50}=0.55 (0.50-0.61)



Carvacryl propionate
LD_{50}=0.65 (0.64-0.66)

Figure 1. Structures and LD_{50} (μmole/fly) of thymol and carvacrol compounds. 95% confidence intervals of LD50 values in parentheses.

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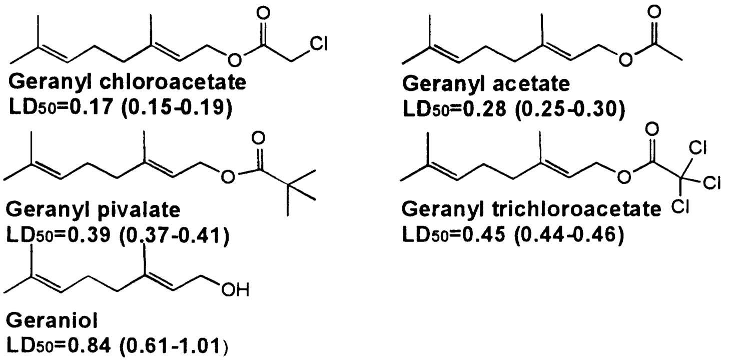
Geraniol Compounds:



Geranyl chloroacetate
LD_{50}=0.17 (0.15-0.19)

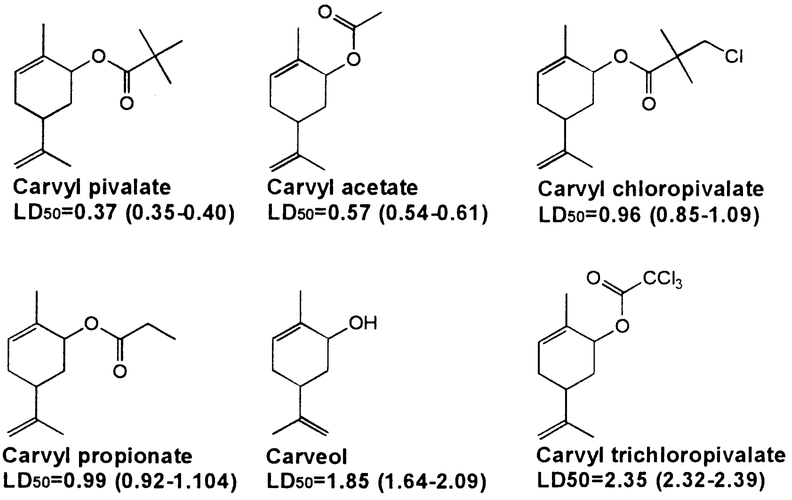
Geranyl acetate
LD_{50}=0.28 (0.25-0.30)

Geranyl pivalate
LD_{50}=0.39 (0.37-0.41)

Geranyl trichloroacetate
LD_{50}=0.45 (0.44-0.46)

Geraniol
LD_{50}=0.84 (0.61-1.01)

Carveol Compounds:



Carvyl pivalate
LD_{50}=0.37 (0.35-0.40)

Carvyl acetate
LD_{50}=0.57 (0.54-0.61)

Carvyl chloropivalate
LD_{50}=0.96 (0.85-1.09)

Carvyl propionate
LD_{50}=0.99 (0.92-1.104)

Carveol
LD_{50}=1.85 (1.64-2.09)

Carvyl trichloropivalate
LD50=2.35 (2.32-2.39)

Figure 2. Structures and LD_{50} (μmole/fly) of geraniol and carveol compounds. 95% confidence intervals of LD50 values in parentheses.

most toxic compounds within its group. There was no obvious trend in structure that helps explain toxicity of these compounds. To help clarify what moieties of the molecules are responsible for their toxicity, we examined classical and quantum parameters to try to explain their toxicity.

Monoterpenoid QSAR analysis

The classical parameters mentioned previously, molar refractivity, molecular connectivity indices (0,1,2), valance connectivity indices (0,1,2), shape indices (1,2,3), and Log P, were calculated by CAChe^{TM} (Oxford Molecular). The quantum parameters, highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), dipole moment (magnitude and direction), Mulliken population, and polarizablitiy, were calculated in GAMESS^{TM}. Geometry and energy of all the molecules were optimized using a split valance basis set and a polarization function (6-31*d) calculation using GAMESS^{TM}. Hessian runs were performed using 6-31*d calculations using GAMESS^{TM} to show that all the molecules tested were at an energy-minimum conformation. Classical and quantum parameters were plotted against house fly LD_{50}s. All regression analyses were fitted using Microsoft Excel^{TM}.

A relationship was not found between all the monoterpenoids (and their derivatives) and their toxicity to house flies. We did find relationships within sub-groups such as, thymol and its derivatives. Thymol compounds, carveol compounds, and carvacrol compounds showed no correlation between classical parameters and toxicity. Log P is often used to explain chemical uptake and hydrophobic interactions between ligand and a receptor. The lack of correlation between Log P and the toxicity of monoterpenoids indicates that changing the ester group does not have a dramatic effect on uptake or hydrophobic interactions. No correlations were found for thymol compounds, carveol compounds, and carvacrol compounds, but there were correlations found between the toxicity of geraniol compounds and molar refractivity, molecular connectivity indices (0,1,2), valance connectivity (0,1,2), and shape indices (1,2,3) (Fig 3). However, the correlation between toxicity and the previously mentioned parameters was a parabolic relationship using only five data points. The parabolic relationships suggest that there is an optimal region for toxicity of that series of derivatives. More data points should be added to verify this relationship. No correlations were found between toxicity and molar refractivity, molecular connectivity indices (0,1,2), valance connectivity (0,1,2), or shape indices (1,2,3), for thymol, carveol, and carvacrol compounds, which indicates that modifying the esters at the –OH position of the monoterpenoids

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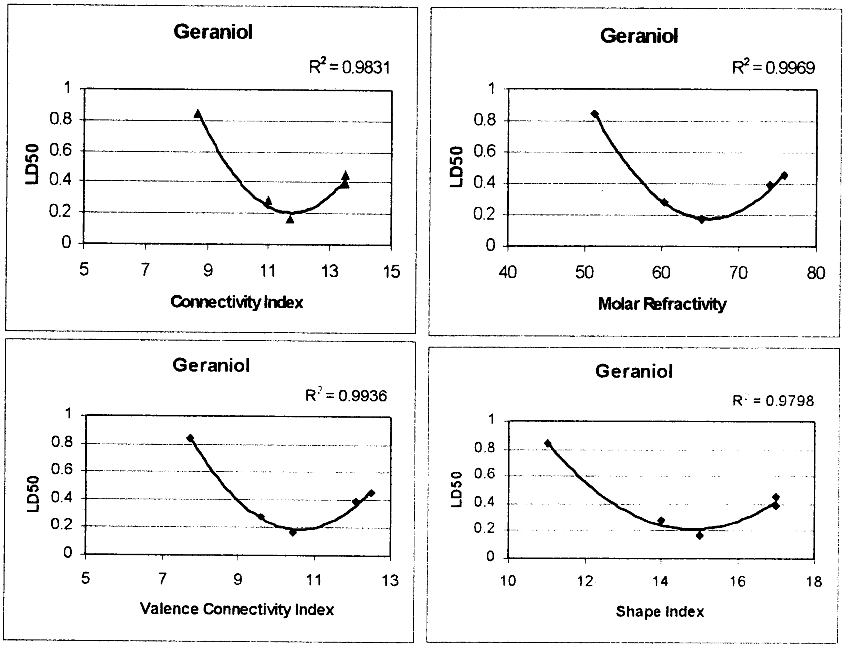

Figure 3. Relationships of geraniol compounds' toxicity with connectivity index (0), molar refractivity valence connectivity index (0), and shape index (1),

does not seem to have a major effect on toxicity. The size or shape of the esters does not seem to be a major factor on toxicity to house flies.

Only one quantum parameter (Mulliken population) showed a correlation between toxicity of thymol, carveol, and carvacrol compounds. Geraniol compounds showed no correlation between their toxicity and any of the quantum parameters. We obtained a correlation between toxicity and Mulliken population within the thymol, carveol, and carvacrol groups. Our study revealed a linear trend of increasing toxicity within the various groups to Mulliken population of certain atoms within that group. Thymol and its derivatives showed a relationship between toxicity and the Mulliken population on three atoms. Thymol compounds revealed that as the Mulliken population around atom 13 increases, toxicity of the compound decreases. The numbers on the atoms for thymol, carvacrol, and carveol correspond to the order the atoms were added to the Z-matrix to construct the molecules (Fig.4). Atom 12 of the thymol compounds showed that as Mulliken population decreased toxicity increased. Atom 11 of the thymol compounds revealed the inverse relationship of atoms 13 and 12. It showed that as Mulliken population increased, toxicity also increased. We obtained an r^2=0.96 for atom 13 with n=6 (Fig. 5). Atom 11 had an r^2=0.83 with n=6 (Fig. 6), and atom 12 had an r^2=0.92 with n=6 (Fig. 7). We also obtained a linear correlation with toxicity and Mulliken population within the carvacrol group. Two atoms within the carvacrol group (6 and 12) showed a relationship between Mulliken population and toxicity. As Mulliken population increases around these atoms, their toxicity also increases. We obtained an r^2=0.78 for atom 6 with an n=6 (Fig. 8), and for atom 12 we obtained an r^2=0.86 with n=6 (Fig. 9). The carveol group of compounds also had a relationship between toxicity and Mulliken population. As the Mulliken population around atom 6 increased, toxicity also increased (r^2=0.86; n=6) (Fig. 10). These correlations demonstrate that the electronic effects of thymol, carveol, carvacrol compounds are important for explaining toxicity.

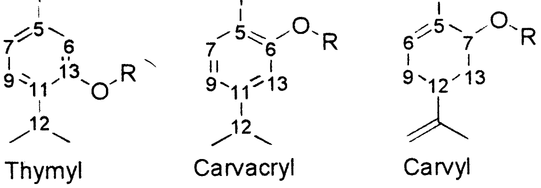

Figure 4. Numbering of the atoms for thymol, carvacrol, and carveol compounds. These numbers correspond to the order they were placed into the Z-matrix.

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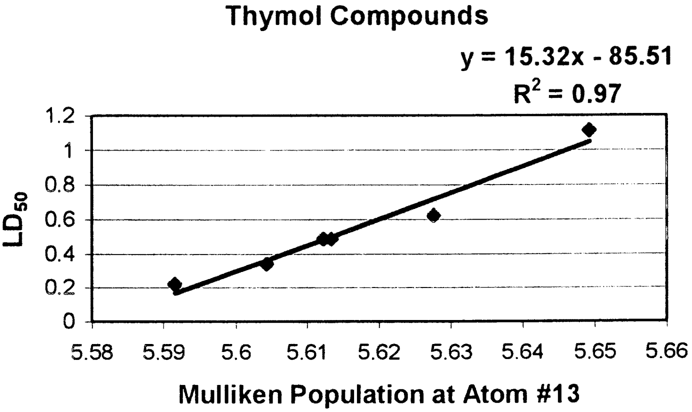

Figure 5. Linear correlation between thymol compounds' house fly toxicity and Mulliken population around atom 13.

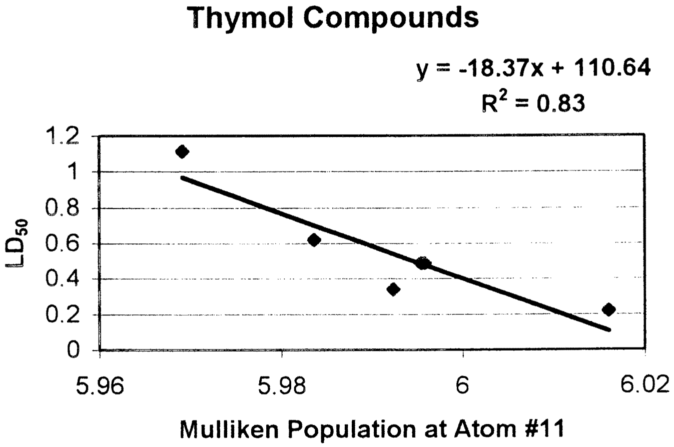

Figure 6. Linear correlation between thymol compounds' house fly toxicity and Mulliken population around atom 11.

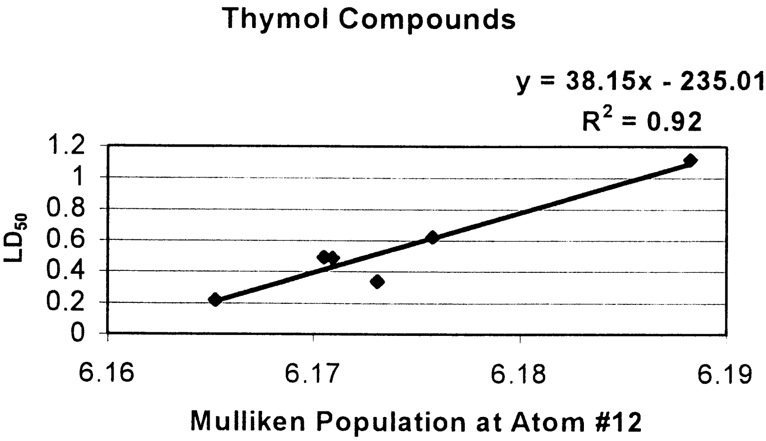

Figure 7. Linear correlation between thymol compounds' house fly toxicity and Mulliken population around atom 12.

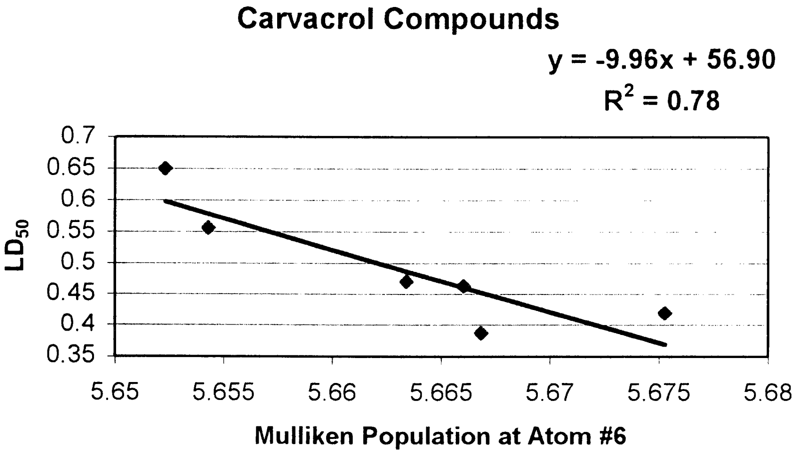

Figure 8. Linear correlation between carvacrol compounds' house fly toxicity and Mulliken population around atom 6.

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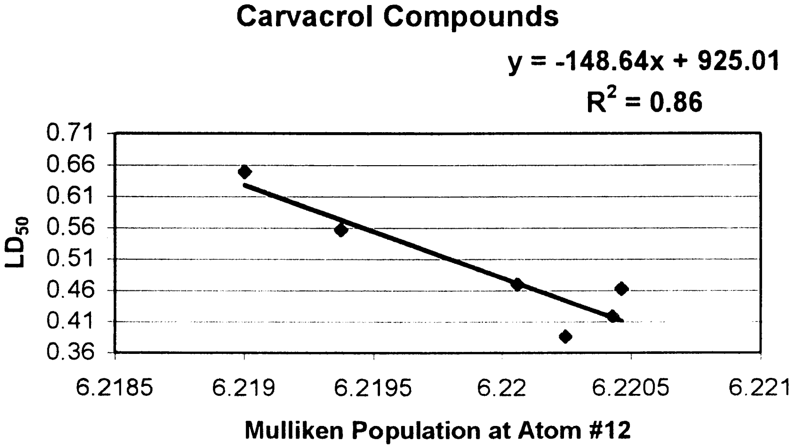

Figure 9. Linear correlation between carvacrol compounds' house fly toxicity and Mulliken population around atom 12.

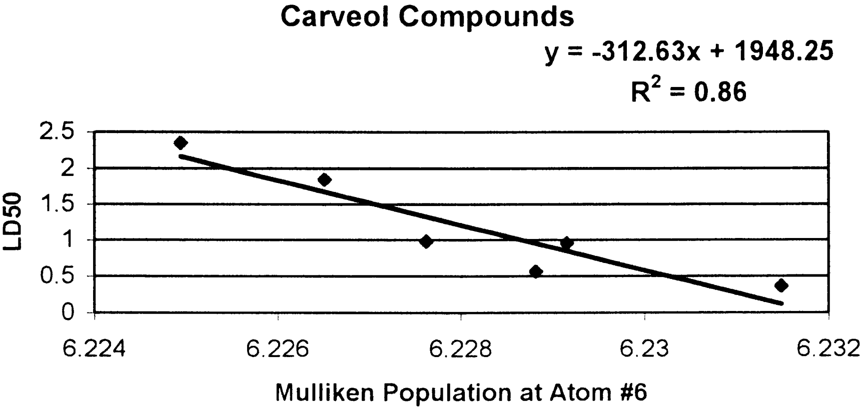

Figure 10. Linear correlation between carveol compounds' house fly toxicity and Mulliken population around atom 6.

Conclusion

No relationship was found between parameters for all the monoterpenoids (and their derivatives) and their toxicity; however we did find relationships for the structure characteristics of sub-groups and their toxicity. Since the sub-groups are not as large or diverse as the whole group the monoterpenoids. further compounds are needed to truly test the validity of these relationships. These smaller sets of relationships give us a good starting point to develop more robust QSARs and also can be used to increase the insecticidal effectiveness of compounds with in the sub-groups.

Geraniol compounds were the only set of monoterpenoids to show a relationship between toxicity and the classical parameters studied. Those classic parameters all encoded information on size and shape of the ester functional group. If these correlations hold true when more compounds are added. we will know that there is an optimal size and shape requirement for that part of the molecule that must be met for the compound to exert its toxic effect on house flies. Since there is a parabolic relationship. we can already predict the optimum toxicity for these compounds. To increase geraniol compounds' toxicity, other regions of the molecules need to be modified.

For thymol, carveol, and carvacrol compounds, Mulliken population around certain atoms in the molecules showed a strong correlation with their toxicity. Mulliken population, which represents the probability of electron population around the atoms in the molecule, may explain electrostatic interactions of the monoterpenoids to a receptor. Regardless of the actual mechanism, the electronic effects of the molecule are important for their toxicity. The classical parameters revealed no correlation with these compounds' toxicity nor any structural parameter examined. This indicates we can modify the –OH region of the molecule. Because size and shape of that part of the molecule does not seem to be important for toxicity. we can add a functional group at that part of the molecule to change the Mulliken population around certain atoms to increase toxicity. In the future. more compounds with different functional groups need to be examined in order to truly validate these QSARs.

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Chapter 24

Chemical and Microbial Modifications of Spinosyn: Exploring Synergies between Fermentation Microbiology and Organic Chemistry

Herbert A. Kirst[1], Lawrence C. Creemer[1], M. Chris Broughton[2], Mary L. B. Huber[3], and Jan R. Turner[4]

[1]Elanco Animal Health Research and Development, 2001 West Main Street,
Greenfield, IN 46140–0708
[2]Pharmaceutical Projects Management, Eli Lilly and Company,
Indianapolis, IN 46285–2148
[3]Animal Health Fermentation Development, Eli Lilly and Company,
Indianapolis, IN 46285–3856
[4]651 Ash Drive, Carmel, IN 46032

Each of the four possible pseudoaglycones and two aglycones of spinosyns A and D were prepared and derivatives were synthesized by modifications at C-9 and C-17. Methods for selective removal of amino or neutral sugar substituents were developed, in some instances using analogs obtained from biosynthetically-blocked strains of the producing organism. Bioconversions using these substrates indicated that more than one biosynthetic sequence was possible to produce spinosyn A from its aglycone. A preferred biosynthetic route for the order of glycosidation and O-methylation was addition of rhamnose on the 9-hydroxyl group, sequential 2'-, 3'-, and 4'-O-methylation, and addition of forosamine on the 17-hydroxyl

group. Semisynthetic derivatives with strong insecticidal activity were obtained by removing the 2'- or 3'-hydroxyl group from several O-demethyl analogs of the spinosyns.

Introduction

The spinosyns are a relatively large family of natural products that were initially discovered during screening operations conducted at the Lilly Research Laboratories in the 1980's (*1*). These fermentation-derived insecticides possess complex macrolide structures that are produced by a novel microorganism, *Saccharopolyspora spinosa* (*2*). The structure of the major factor, spinosyn A, is comprised of a polyketide-derived tetracyclic ring system to which is attached an amino sugar (β-D-forosamine) and a neutral sugar (α-L-2,3,4-tri-O-methylrhamnose) (Figure 1) (*3*). The second most abundant factor, spinosyn D, differs by the presence of a methyl substituent on the double bond at C-6 (*3*). These two factors are the predominant active components in the naturally occurring insecticidal mixture known under the generic name, spinosad, and sold by Dow AgroSciences under the trade name, Tracer®(*4, 5*).

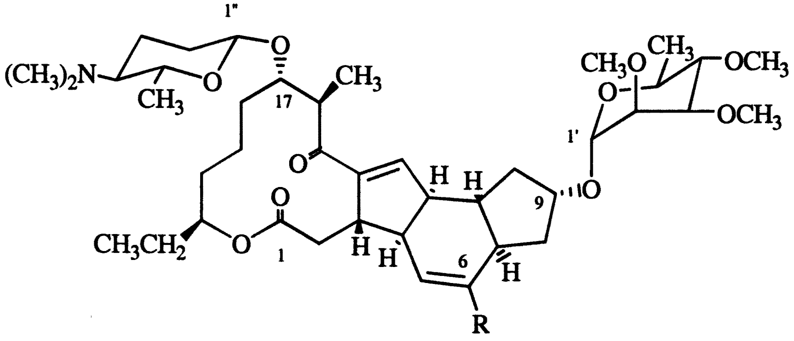

Figure 1. Structures of spinosyn A (R = H) and spinosyn D (R = CH_3).

In the course of fermentation development studies directed toward improving the titer of spinosyns A and D, various mutant strains of *S. spinosa* were discovered that produced larger amounts of different factors that varied in

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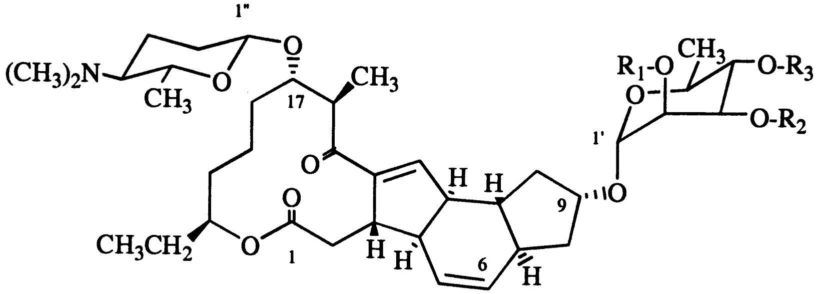
the degree of O-methylation of the rhamnosyl moiety (Figure 2) (*5-7*). These biosynthetically-blocked mutant strains allowed access to some of these factors in multi-gram quantities, making them especially valuable for chemical modification efforts that were not readily accomplished starting from spinosyns A and D themselves. From these starting materials, several deoxy-rhamnosyl derivatives were readily synthesized that exhibited potent insecticidal activity against the assay organism, *Heliothis virescens*. In addition, some other new semisynthetic derivatives were useful for studies to explore bioconversions and to elucidate biosynthetic pathways.



Spinosyn H: $R_1 = H$; $R_2 = R_3 = CH_3$
Spinosyn J: $R_2 = H$; $R_1 = R_3 = CH_3$
Spinosyn K: $R_3 = H$; $R_1 = R_2 = CH_3$
Spinosyn T: $R_1 = R_2 = H$; $R_3 = CH_3$
Spinosyn U: $R_1 = R_3 = H$; $R_2 = CH_3$
Spinosyn P: $R_2 = R_3 = H$; $R_1 = CH_3$

Figure 2. Structures of O-demethyl analogs of spinosyn A.

Synthesis and Bioconversions of Pseudoaglycones

Acid-catalyzed hydrolysis [1N H_2SO_4, 80°] of forosamine from spinosyns A, D, H, J, or K yielded the corresponding 17-pseudoaglycones (17-Psa A, D, H, J, or K, respectively) in 60-90% yields (Figures 3 and 4). Bioconversion of each pseudoaglycone by *S. spinosa* re-formed each corresponding parent compound except for 17-Psa K, which gave spinosyn A rather than spinosyn K as its product (Figure 4). These results suggested that forosamine could be attached as the final biosynthetic step in the formation of the spinosyns and that 4'-O-methylation is the last of the three O-methylations of rhamnose to occur.

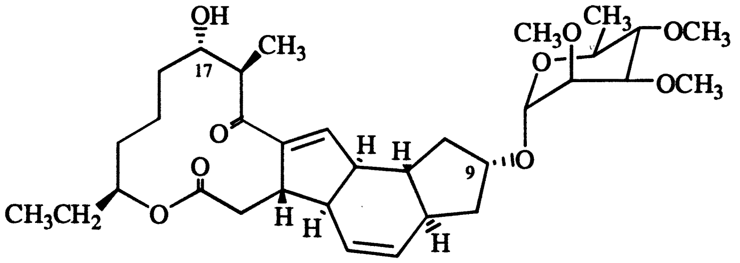


Figure 3. Structure of 17-Psa A.

Spinosyn A $\xrightarrow{H^+}$ 17-Psa A $\xrightarrow{S.\ spinosa}$ Spinosyn A

Spinosyn D $\longrightarrow$ 17-Psa D $\longrightarrow$ Spinosyn D

Spinosyn H $\longrightarrow$ 17-Psa H $\longrightarrow$ Spinosyn H

Spinosyn J $\longrightarrow$ 17-Psa J $\longrightarrow$ Spinosyn J

Spinosyn K $\longrightarrow$ 17-Psa K $\longrightarrow$ Spinosyn A

Figure 4. Formation and bioconversion of 17-pseudoaglycones.

Several attempts were made to use bioconversions as a means to efficiently prepare novel derivatives. However, neither *Streptomyces thermotolerans* nor *Streptomyces fradiae* (producers of the 16-membered macrolide antibiotics, carbomycin and tylosin, respectively) performed any bioconversion of 17-Psa A. Swern oxidation of the 17-hydroxyl group of 17-Psa A [NCS, iPr_2S, Et_3N, CH_2Cl_2, -78°] yielded the 17-keto derivative, which was then reduced [$NaBH_4$, MeOH, r.t.] to give the 17-β-hydroxy epimer. However, neither of these latter two compounds was bioconverted by *S. spinosa*, indicating that this organism does not contain a 17-reductase that reduces this 17-keto substrate and the correct (α) stereochemistry of the 17-hydroxyl group is critical for the compound to be accepted for glycosidation.

In addition to the three di-O-methyl analogs, the three possible mono-O-methyl analogs have also been isolated from culture broths of mutant strains (Figure 2) (*5-7*). However, the 9-O-rhamnosyl analog has not yet been found as

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a naturally-occurring factor, so its chemical synthesis became of interest. To accomplish this synthesis, the 9-pseudoaglycone of spinosyn A (9-Psa A, Figure 5) was required, which meant that hydrolysis of the neutral sugar was necessary using conditions under which the highly acid-labile amino sugar would remain intact. For this task, spinosyn J provided the necessary means. Swern oxidation of the 3'-hydroxyl group [NCS, iPr_2S, Et_3N, CH_2Cl_2, -78°] produced the corresponding 3'-ketone, from which the neutral sugar was readily removed by base-catalyzed elimination [K_2CO_3, MeOH, r.t.] to give the desired 9-Psa A (*8*).

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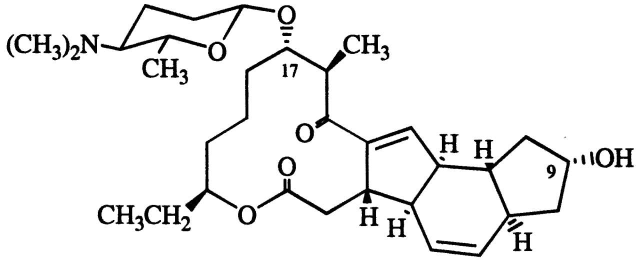

Figure 5. Structure of 9-Psa A.

Bioconversion of 9-Psa A by *S. spinosa* also yielded spinosyn A, demonstrating that either sugar could be attached as the final biosynthetic step. The 9-hydroxyl group of 9-Psa A was oxidized using the same Swern conditions as before and subsequent reduction of the 9-ketone by $NaBH_4$ provided an approximate 1:1 mixture of the two 9-epimeric alcohols. However, analogous to results from the C-17 derivatives, neither the 9-ketone nor the epimeric 9-hydroxyl analog was bioconverted, indicating that *S. spinosa* does not contain a 9-reductase that reduces this ketone and the natural (α) stereochemistry of the 9-hydroxyl group is essential for the compound to be accepted for glycosidation.

Commercially available L-(+)-rhamnose was converted to its 1-bromo-2,3,4-tri-O-acetyl derivative by standard methods and was then successfully coupled with 9-Psa A [AgOTf, $(Me_2N)_2CO$, CH_2Cl_2, 15%; then deacetylation by NaOMe, MeOH, r.t., 86%] to give the 9-O-rhamnosyl derivative of 9-Psa A, albeit in low yield (*9*). Alternative glycosidation conditions [*e.g.*, AgOTf, DIPEA, CH_2Cl_2] yielded the often-expected orthoester derivative rather than the desired α-glycosyl derivative (*10*). Bioconversion of the 9-O-α-rhamnosyl analog successfully produced spinosyn A, indicating that the neutral sugar at C-9 is very likely attached as rhamnose, and subsequent O-methylation can occur with forosamine already attached at C-17.

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Synthesis and Bioconversions of Aglycones

Hydrolysis of 17-Psa A under more vigorous acidic conditions [7.2N H_2SO_4, MeOH, reflux] successfully cleaved tri-O-methylrhamnose and produced the corresponding aglycone (*8*). However, when these same conditions were applied to 17-Psa D, only a mixture of decomposition products was obtained (Figure 6). The most likely explanation for this greater reactivity is that the methyl group at C-6 in spinosyn D allows more facile protonation of the double bond by formation of a tertiary carbonium ion at C-6, which subsequently undergoes bond migrations and skeletal rearrangements. However, the availability of spinosyn L (6-methyl analog of spinosyn J) from the fermentation of mutant strains permitted the formation of 9-Psa D by the route analogous to that described above for 9-Psa A. Subsequent removal of forosamine from 9-Psa D then readily occurred under mild acidic conditions to yield the aglycone of spinosyn D (Figure 6) (*8*).

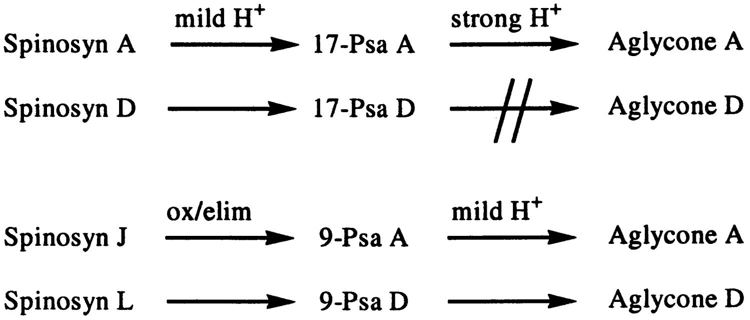

Figure 6. Formation of pseudoaglycones and aglycones.

The aglycone of spinosyn A was successfully bioconverted by *S. spinosa* to spinosyn A, but some 17-Psa A was also found, suggesting that attachment of forosamine may be the rate-limiting final step in the biosynthetic pathway. Although the 9-keto derivative of the aglycone (*11*) was not bioconverted, the 17-keto derivative of the aglycone showed evidence for addition of rhamnose by mass spectral analysis. This result suggested that attachment of rhamnose might be the first biosynthetic step after formation of the aglycone (Figure 7). The fourth structural permutation, the 9,17-bis-keto derivative of spinosyn A (*11*), was not bioconverted by *S. spinosa*.

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Biosynthetic Pathway to Spinosyn A

The available evidence from the bioconversion experiments supports several possible biosynthetic pathways leading from aglycone to spinosyn A. Although not definitively proven, the suggested preferred pathway starting from the aglycone involves 1) addition of rhamnose to the C-9 hydroxyl group, 2) sequential 2'-, 3'-, and then 4'-O-methylation, and 3) addition of forosamine to the C-17 hydroxyl group (Figure 7).

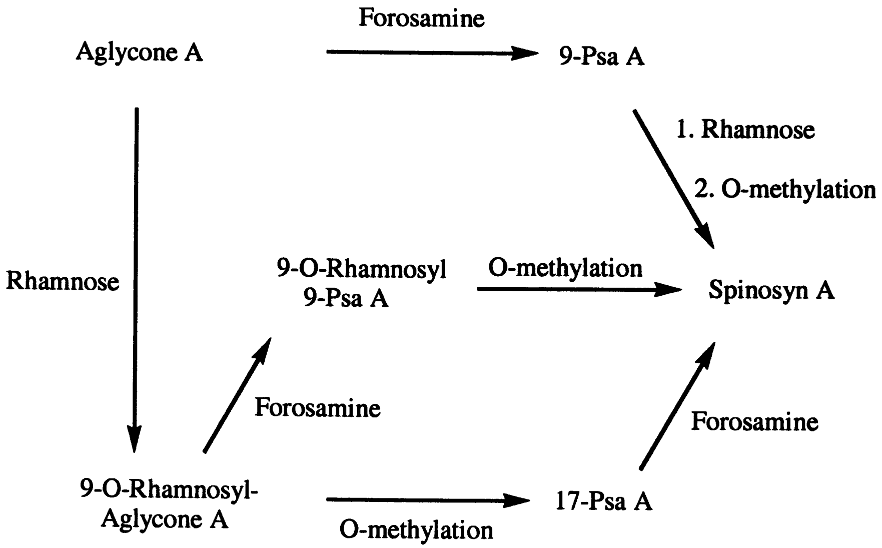
Aglycone A
Forosamine
9-Psa A
1. Rhamnose
2. O-methylation
Rhamnose
9-O-Rhamnosyl 9-Psa A
O-methylation
Spinosyn A
Forosamine
Forosamine
9-O-Rhamnosyl-Aglycone A
O-methylation
17-Psa A

Figure 7. Possible biosynthetic routes for glycosidation and O-methylation.

5,6-Epoxy Derivatives

While exploring other modifications during SAR studies, epoxidation of 17-Psa A was performed [MCPBA, CH_2Cl_2], from which a mixture of the 5,6-α- and β-epoxides was isolated. This mixture of epoxides was bioconverted by *S. spinosa* to a corresponding mixture of 5,6-α- and β-epoxides of spinosyn A. The product was identified by comparison with the 8:1 mixture of β- and α-epoxides that had been synthesized from spinosyn A by analogous MCPBA epoxidation and subsequent selective reduction of the 5,6-epoxy-4''-N-oxide intermediate using an oxygen transfer reaction with triphenylborane in chloroform (*12*). This successful bioconversion result represents the first example of acceptance and bioconversion of an unnatural substrate by *S. spinosa*.

Modifications of Spinosyns H, J, and K

The availability of multi-gram quantities of spinosyns H, J, and K also made them of interest as starting materials for SAR investigations. Acetylation of the free hydroxyl group in each compound under standard conditions (Ac_2O, Pyr) yielded the corresponding 2'-, 3'-, or 4'-O-acetyl derivatives of spinosyns H, J, and K, respectively (*13*). In each case, the LD_{50} values measuring lethality toward neonate tobacco budworm (*Heliothis virescens*) were lower for the O-acetyl derivative compared to its respective parent compound (Table I), indicating substitutions of the free hydroxyl group may be generally beneficial for improving efficacy. Consequently, deoxygenation of each compound was investigated next, utilizing Barton-type chemistry for removal of the different hydroxyl groups. To accomplish these transformations, spinosyns H, J, and K were each converted to their respective xanthates [1) NaH, cat. imidazole, THF; 2) CS_2; 3) CH_3I] followed by reductive cleavage [Bu_3SnH, cat. AIBN, toluene, reflux] to produce the corresponding 2'-, 3'-, or 4'-deoxy derivatives of spinosyns H, J, and K, respectively (*13*). The LD_{50} values vs. neonate *H. virescens* were substantially lowered for 2'-deoxy spinosyn H and 3'-deoxy spinosyn J, whereas the effect was minimal for 4'-deoxy spinosyn K (Table I).

Table I. LD_{50} Values vs. Neonate *H. virescens* (Spinosyn A: 0.3 ppm)

Spinosyn H Series		*Spinosyn J Series*		*Spinosyn K Series*	
2'-OH	3.2 ppm	3'-OH	>80 ppm	4'-OH	3.5 ppm
2'-O-acetyl	1.2 ppm	3'-O-acetyl	33 ppm	4'-O-acetyl	1.3 ppm
2'-xanthate	14.6 ppm	3'-xanthate	0.7 ppm	4'-xanthate	24 ppm
2'-deoxy	<0.4 ppm	3'-deoxy	0.4 ppm	4'-deoxy	4.1 ppm

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Fermentation of mutant strains of *S. spinosa* had also made available the three possible 6-methyl (*i.e.*, D-ring aglycone) analogs of spinosyns H, J, and K, which have been designated as factors Q, L, and O, respectively (*5-7*). Since spinosyn Q has been one of the most active natural factors against *H. virescens* (*6, 7*), it was especially of interest to synthesize its 2'-deoxy derivative. If the activity were to be improved over the parent factor by an order of magnitude analogous to the improvement obtained from 2'-deoxy-spinosyn H, it would result in an extremely potent new derivative. Following the same methodology used previously, spinosyn Q and spinosyn L were each converted to their 2'- and 3'-deoxy derivatives, respectively, and tested for insecticidal activity (Table II).

Table II. LD_{50} Values vs. Neonate *H. virescens*

		[Aglycone of A]	*[Aglycone of D]*
2'	*3'*	*C-6 Substituent: H*	*C-6 Substituent: CH_3*
OCH_3	OCH_3	0.31 ppm (Spinosyn A)	0.8 ppm (Spinosyn D)
OH	OCH_3	3.2 ppm (Spinosyn H)	0.39 ppm (Spinosyn Q)
H	OCH_3	0.23 ppm (2'-Deoxy-H)	0.23 ppm (2'-Deoxy-Q)
OCH_3	OH	>80 ppm (Spinosyn J)	26 ppm (Spinosyn L)
OCH_3	H	0.36 ppm (3'-Deoxy-J)	0.27 ppm (3'-Deoxy-L)

Although the activity against *H. virescens* was substantially improved for 3'-deoxy-spinosyn L, it was only slightly improved for 2'-deoxy-spinosyn Q and was essentially the same as 2'-deoxy spinosyn H. Despite significant differences in activity exhibited by the various parent factors, the four 2'- and 3'-deoxy derivatives exhibited activities essentially equivalent to each other as well as to spinosyn A. Subsequent follow-up testing of the derivatives did not reveal any significant differences that justified their commercial development.

Conclusions

These results provide another example in which biosynthetically-blocked mutant strains of a secondary metabolite-producing microorganism provided access to useful new structural modifications (*14, 15*). In the present case, the availability of compounds derived from such mutant strains enabled convenient syntheses of new derivatives that are difficult to obtain from spinosyn A itself. Thus, the efforts of microbiologists to identify biosynthetically-blocked mutants can provide organic chemists with useful starting materials for synthetic studies. In return, some of the new semisynthetic derivatives may be employed for bioconversion studies or for elucidation of biosynthetic pathways. Thus, each discipline benefits from the other and enables investigations that would be more difficult to conduct if each discipline operated solely by itself. The availability of useful amounts of mutant-derived compounds also benefits medicinal chemistry studies of structure-activity relationships. In the present case, it enabled the synthesis of a series of new derivatives of spinosyns that exhibited potent insecticidal activity. Finally, the biosynthetic and SAR information should be useful for the design of additional novel compounds by the emerging technologies of microbial genetic engineering and combinatorial biosynthesis, which are particularly applicable to polyketide-derived natural products such as the spinosyns (*16-18*).

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Chapter 25

Rhamnose Replacement Analogs of Spinosyn A

P. B. Anzeveno and F. R. Green, III

Discovery Research Center, Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268–1053

This chapter describes the syntheses and bioactivities against tobacco budworm (TBW) and two-spotted spider mite (TSSM) of a number of rhamnose replacement analogs of spinosyn A; compounds in which the rhamnose has been replaced by other sugars, methoxybenzoic acids, methanol and 2-methoxyethanol. The sugar replacements include α- and β-linked pyranoses and furanoses: D-rhamnose, 2-deoxy-L-rhamnose, L-lyxose, L-ribose, L-mannose, L-(3-*O*-L-rhamnosyl)rhamnose and *N*-demethyl-D-forosamine. The D-sugar-, β-anomeric sugar-, furanose sugar-, α, α'-disaccharide, forosaminyl- and non-sugar analogs were inactive against both TBW and TSSM. The α,β'-disaccharide retained activity against TBW. Removal of the 6-methyl group (L-lyxose analog) did not significantly affect activity, while addition of a methoxyl to the 6-methyl group (L-mannose analog) led to an ~ 10-fold enhancement of TBW activity. The 2-deoxyrhamnose analogs showed somewhat enhanced TBW activity but no TSSM activity.

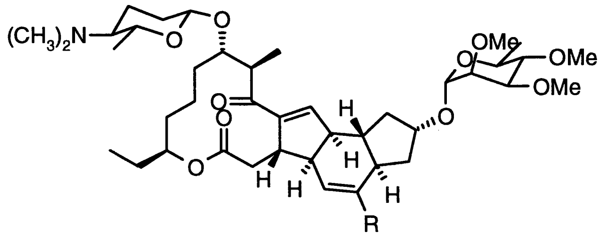
The spinosyns (Figure 1) are a new family of insecticidal, fermentation-derived macrocyclic lactones produced by a novel actinomycete, *Saccharopolyspora spinosa* (*1*). The major products produced are spinosyn A and spinosyn D which are present in an approximate 85:15 ratio and which together account for over 90% of the active material (2). Currently, more than 24 natural spinosyns have been isolated and characterized. These differ

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

predominantly in the methylation patterns of the amine and hydroxyl groups and to a lesser extent in the C-methylation of the nucleus. These natural factors have been evaluated and their relative insecticidal activities reported (*3*).

When tested against a wide range of insect pests, the spinosyns were found to be extremely effective at controlling primarily lepidopteran insects, major agronomic pests in such crops as cotton and vegetables. Moreover, most other characteristics necessary for effective pest control such as environmental compatibility, speed of action and low toxicity both to mammals and beneficial insects were ideal.

The spinosyns appear to exert their effects on insects through alteration of nicotinic acetylcholine receptor function by a mechanism different from other nicotinic agents such as imidacloprid (*4*). Some effects on the GABA-gated cloride channel system have also been observed.



spinosyn A R = H
spinosyn D R = CH_3

Figure 1.The two major spinosyns

Chemical Modification of the Spinosyns

The insecticidal spectrum exhibited by the spinosyns is quite broad: control of lepidoptera, diptera, mites, aphids, cockroaches, termites and many other species has been seen. However as mentioned above, the greatest activity is against lepidopteran pests such as tobacco budworm and beet armyworm.

At Dow AgroSciences, an extensive chemical modification program was undertaken to identify analogs with enhanced and/or broader spectrum activities. The general spinosyn structure (Figure 2) shows the degree of complexity of the molecule and also suggests sites of potential modification. Each of these sites has been investigated and a general review of both the chemistry and the effects of particular modifications on insecticidal activity has appeared (*5*).

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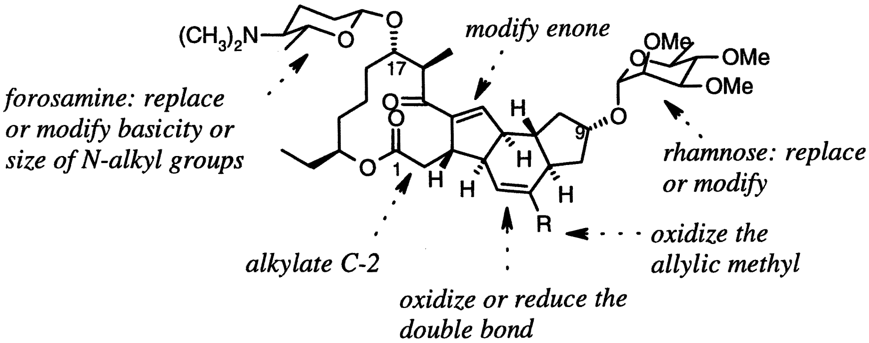

forosamine: replace or modify basicity or size of N-alkyl groups

modify enone

rhamnose: replace or modify

oxidize the allylic methyl

alkylate C-2

oxidize or reduce the double bond

Figure 2. Potential sites of modification of spinosyns

Rhamnose Replacement

This chapter has as its focus, rhamnose replacement analogs of the spinosyns. This work was given impetus by an artificial neural network (ANN)-based QSAR study that predicted that the 2',3',4'-tri-*O*-ethylrhamnopyranosyl analog of spinosyn A would be significantly more active than its parent *and* the subsequent finding that it was indeed 6-13 times more active in a series of bioassays (*6*).

The various rhamnose replacements (Figure 3) were chosen to learn what the effect on activity would be if:

- A D-sugar were substituted for the L (D-rhamnose)
- The sugar was β-linked to the pseudoaglycone (2,3,4-tri-O-ethyl-β-L-rhamnose)
- The 6-methyl group was removed (L-lyxose)
- The 6-methyl group was oxygenated (L-mannose)
- A furanose sugar was substituted (L-ribose)
- A disaccharide was in place ((3-*O*-L-rhamnopyranosyl)-α-L-rhamnose)
- The 2-oxygen was removed (2-deoxy-L-rhamnose)
- A forosamine derivative was substituted (*N*-demethyl forosamine)
- The substitution was by a non-sugar (methoxybenzoic acid, methanol, 2-methoxyethanol).

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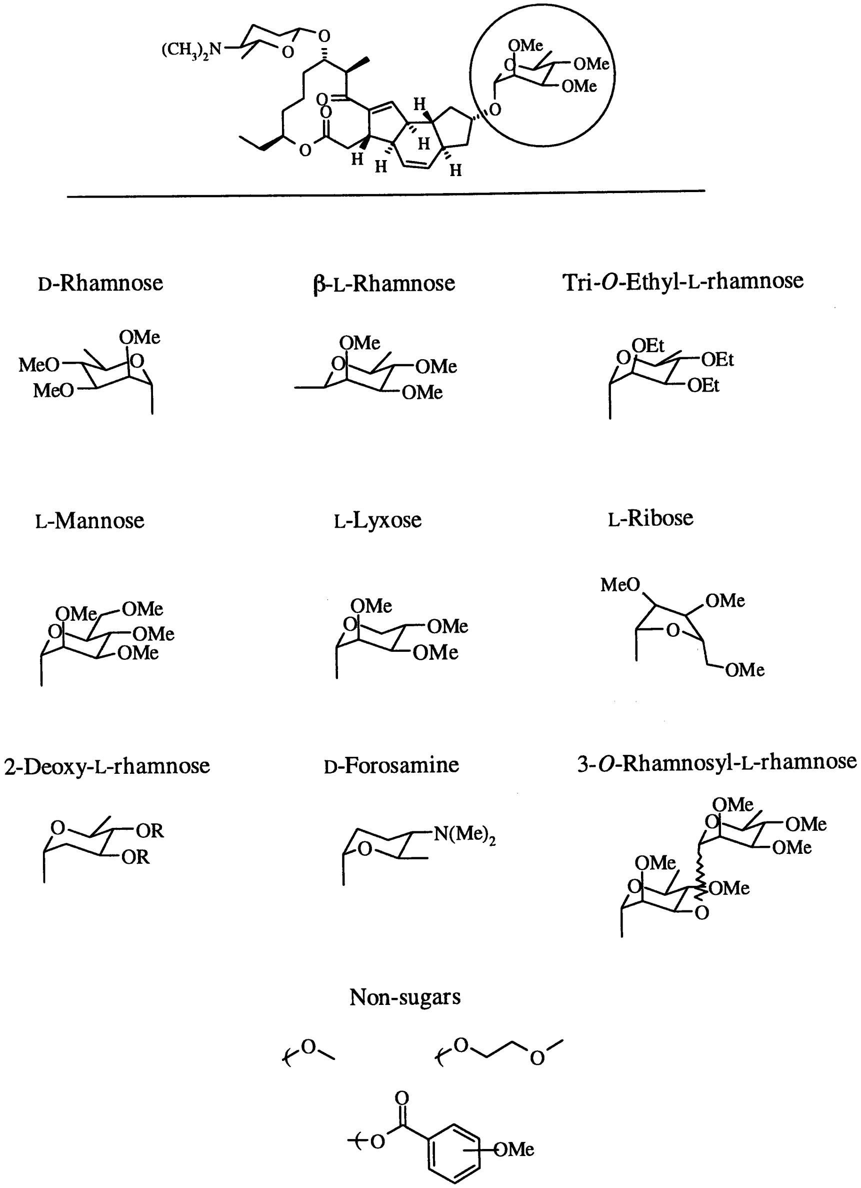
D-Rhamnose
β-L-Rhamnose
Tri-*O*-Ethyl-L-rhamnose
L-Mannose
L-Lyxose
L-Ribose
2-Deoxy-L-rhamnose
D-Forosamine
3-*O*-Rhamnosyl-L-rhamnose
Non-sugars

Figure 3. Rhamnose replacements

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It should be mentioned here that while this work was in progress, work was being done with modification of the rhamnose as its aim, *i.e.*, inverting the stereochemistry of the various hydroxyls, substituting halogens for the hydroxyls, oxidizing the hydroxyls to ketones, *etc.*, all this on the intact spinosyn. These compounds were designated as rhamnose *modified* analogs, to differentiate them from the rhamnose *replacement* analogs discussed herein. The chemistry and activities of these modified analogs has been reported (*7*).

It was known from prior work that for maximum activity any hydroxyl of the "new" sugar would have to be alkylated: compounds with free or acylated hydroxyl groups showed diminished activity (*7*). All of the sugar analogs were prepared as shown in Figure 4 , *i.e.*, by Lewis acid-catalyzed coupling of spinosyn A 9-pseudoaglycone (Psa) with a C-1 activated sugar, most activated as their 1-*O*-trichloroacetimidates. The couplings always generated mixtures of anomers with the α predominating, usually by ~ 4-fold. These were then separated by reversed-phase hplc.

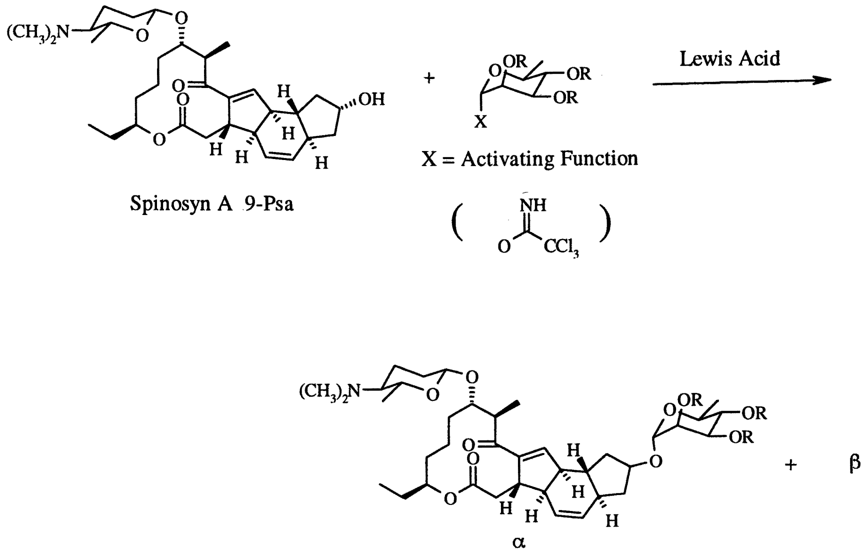

Figure 4

As conditions for the selective hydrolytic removal of the rhamnose sugar from spinosyn A have, as yet, not been found, it was necessary that the 9-pseudoaglycone be obtained either from spinosyn J (the 3'-*O*-demethyl derivative of spinosyn A) or from spinosyn H (the 2'-*O*-demethyl dervative), each produced selectively by mutated strains of *S. spinosa* (*8*). The route from

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spinosyn J has recently been published (*9*). The route from H is disclosed in the spinosyn analog patent (*7*). Both are outlined in Figure 5.

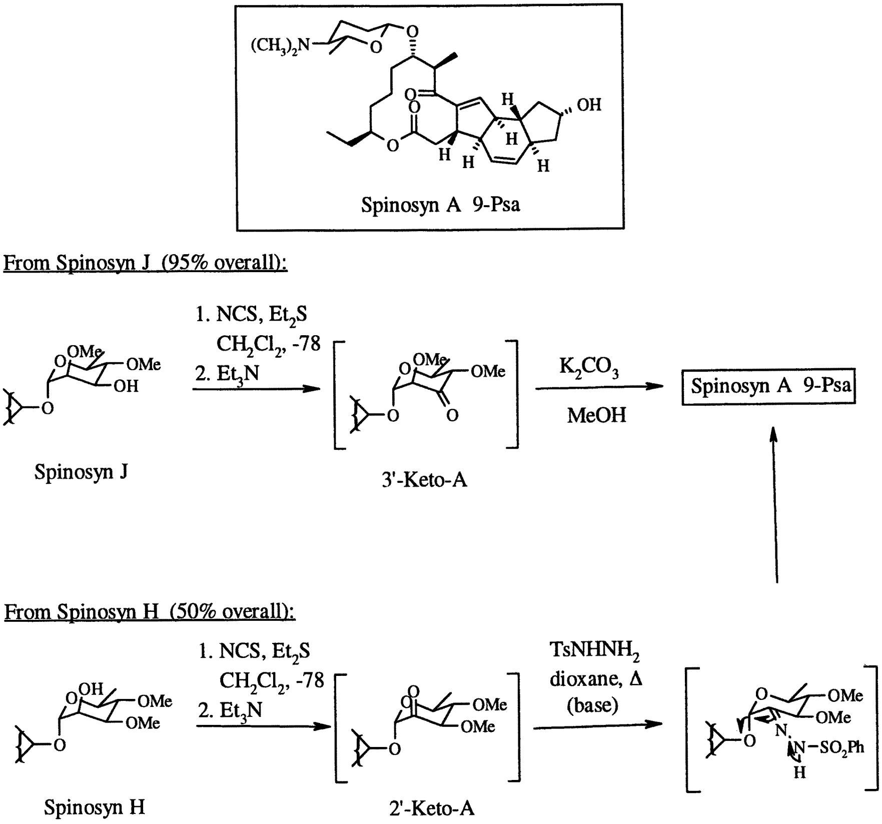
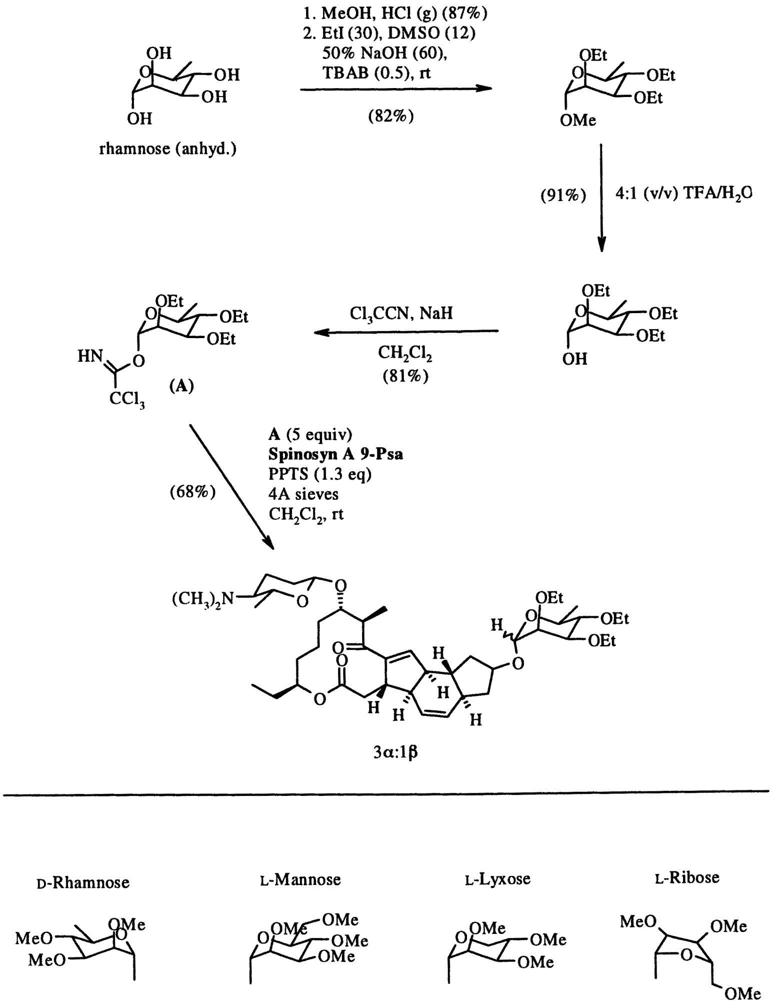

(CH3)2N
O
O
O
O
O
H
H
H
H
H
OH
Spinosyn A 9-Psa
From Spinosyn J (95% overall):
1. NCS, Et2S
CH2Cl2, -78
2. Et3N
OMe
OMe
OH
O
Spinosyn J
3'-Keto-A
K2CO3
MeOH
Spinosyn A 9-Psa
From Spinosyn H (50% overall):
1. NCS, Et2S
CH2Cl2, -78
2. Et3N
OH
OMe
OMe
Spinosyn H
2'-Keto-A
TsNHNH2
dioxane, Δ
(base)
N
N-SO2Ph
H

Figure 5. Preparation of Spinosyn A 9-Psa

Tri-*O*-ethylrhamnose and other Sugar Analogs

The synthesis of the tri-*O*-ethylrhamnose analog is outlined in Figure 6 and is illustrative for the preparations of the per-*O*-methylated D-rhamnose, L-lyxose, L-ribose and L-mannose analogs. Per-*O*-ethylation of methyl rhamnoside was tricky, with the best conditions found, the phase-transfer catalysis procedure described by Nouguier (*10*).The best conditions found for per-*O*-methylation were those used by Evans (trimethyloxonium tetrafluoroborate/proton-sponge) in his synthesis of D-rhamnose (*11*), summarized in Figure 7.



rhamnose (anhyd.)
1. MeOH, HCl (g) (87%)
2. EtI (30), DMSO (12)
50% NaOH (60),
TBAB (0.5), rt
(82%)
(91%)
4:1 (v/v) TFA/H$_2$O
Cl$_3$CCN, NaH
CH$_2$Cl$_2$
(81%)
(A)
A (5 equiv)
Spinosyn A 9-Psa
PPTS (1.3 eq)
4A sieves
CH$_2$Cl$_2$, rt
(68%)
3α:1β
D-Rhamnose
L-Mannose
L-Lyxose
L-Ribose

Figure 6

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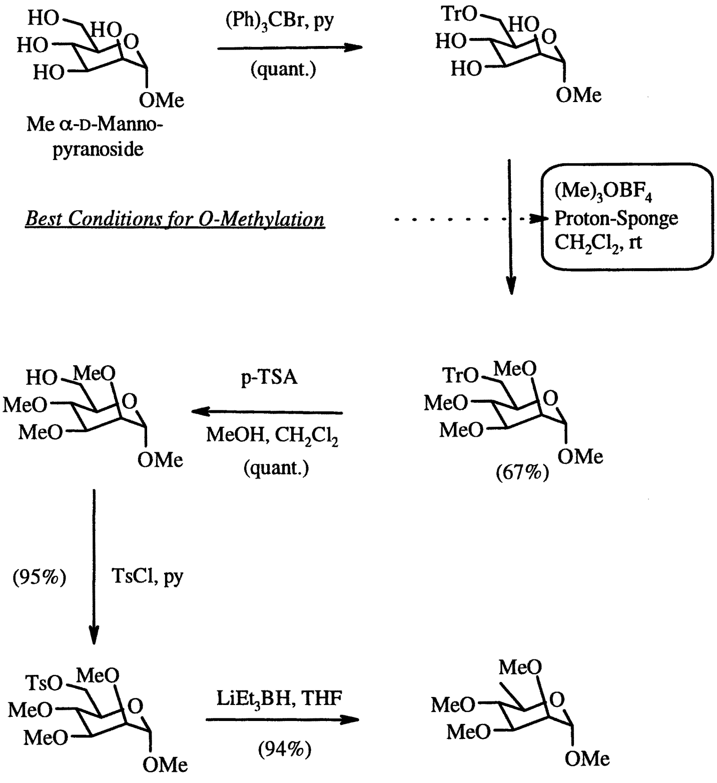
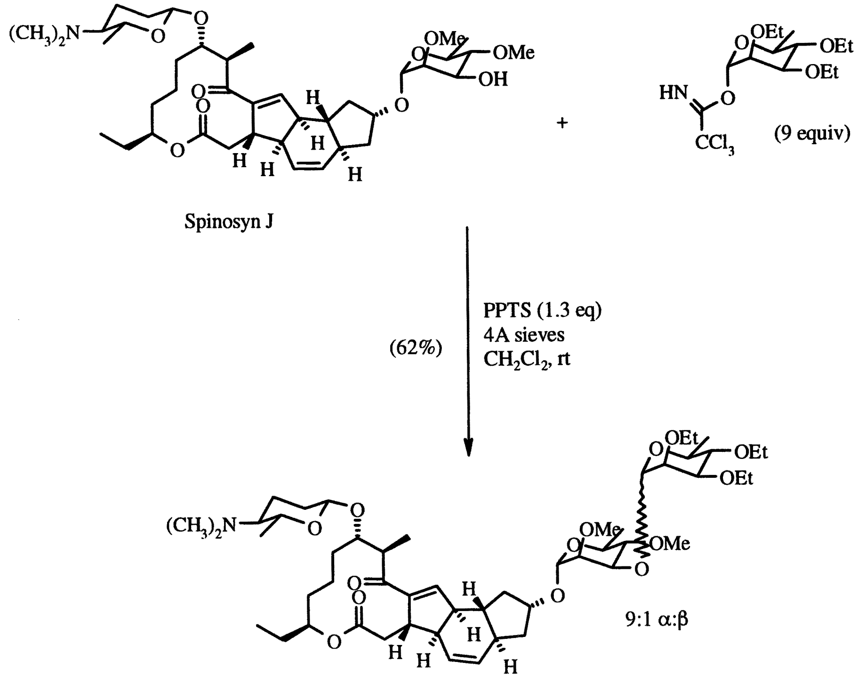

HO
HO
HO
HO
O
OMe
Me α-D-Manno-pyranoside
(Ph)$_3$CBr, py
(quant.)
TrO
HO
HO
HO
O
OMe
Best Conditions for O-Methylation
(Me)$_3$OBF$_4$
Proton-Sponge
CH$_2$Cl$_2$, rt
HO
MeO
MeO
MeO
O
OMe
p-TSA
MeOH, CH$_2$Cl$_2$
(quant.)
TrO
MeO
MeO
MeO
O
OMe
(67%)
(95%)
TsCl, py
TsO
MeO
MeO
MeO
O
OMe
LiEt$_3$BH, THF
(94%)
MeO
MeO
MeO
O
OMe

Figure 7. Best conditions for per-O-methylation

3'-*O*-(2,3,4-Tri-*O*-ethyl-L-rhamnopyranosyl)spinosyn J.

The disaccharide replacement analog, 3'-*O*-(2,3,4-tri-*O*-ethyl-L-rhamnopyranosyl)spinosyn J was prepared as a 9:1 α:β mixture of anomers as summarized in Figure 8.



Spinosyn J

Figure 8

2-Deoxyrhamnose Analogs

The di-*O*-alkylated 2-deoxyrhamnose analogs were prepared in moderate yields, as shown in Figure 9, by coupling of the 9-pseudoaglycone with the respective di-*O*-alkylated rhamnals prepared from 3,4-di-*O*-acetyl-L-rhamnal by phase-transfer catalyzed reaction with an excess of alkyl iodide. The deoxy-diacetate analog was prepared in only 10% yield by coupling of the 9-pseudoaglycone with the 1-(*O*,*O*-diethyldithiophosphoryl) derivative of the deoxy-diacetylated rhamnose. This route was necessitiated as all attempts at acid catalyzed coupling of the diacetylated rhamnal with the pseudoaglycone gave only the Ferrier coupled product, 9-*O*-(4-*O*-acetyl-2,3-dideoxy-2,3-didehydro-L-rham-nosyl) spinosyn A 9-Psa.

Kirst et al. have recently published the preparation of the 2-deoxy analogs of spinosyns A and D by tributyltin hydride mediated deoxygenation of xanthates of the minor spinosyn factors H and Q (*12*).

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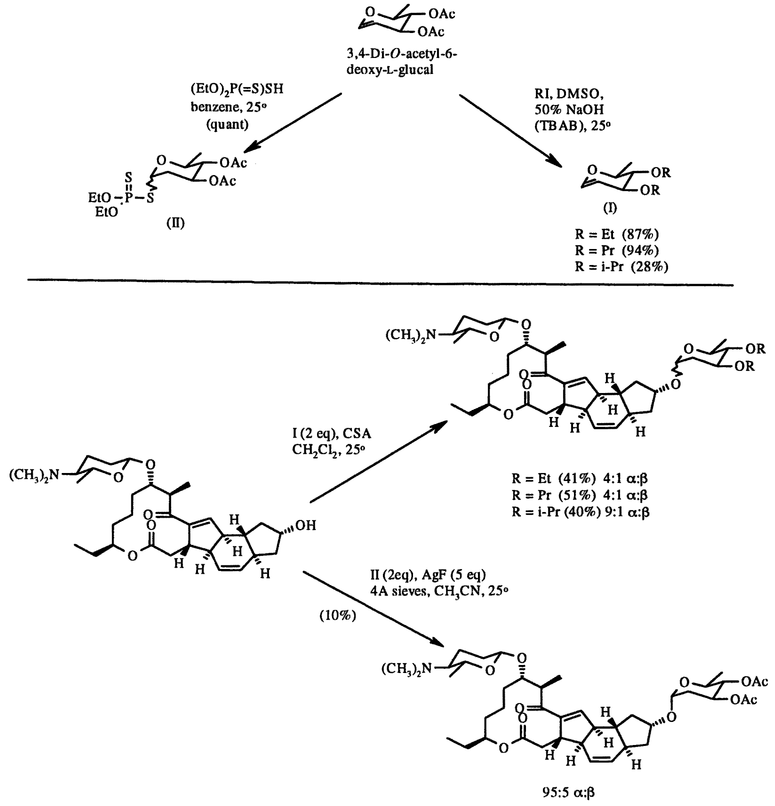
OAc
OAc
3,4-Di-O-acetyl-6-deoxy-L-glucal
(EtO)2P(=S)SH
benzene, 25°
(quant)
RI, DMSO,
50% NaOH
(TBAB), 25°
OAc
OAc
EtO-P-S
EtO
S
(II)
OR
OR
(I)
R = Et (87%)
R = Pr (94%)
R = i-Pr (28%)
(CH3)2N
I (2 eq), CSA
CH2Cl2, 25°
OH
H
R = Et (41%) 4:1 α:β
R = Pr (51%) 4:1 α:β
R = i-Pr (40%) 9:1 α:β
II (2eq), AgF (5 eq)
4A sieves, CH3CN, 25°
(10%)
OAc
OAc
95:5 α:β

Figure 9

9-O-(N-Demethylforosaminyl) Analog

The 9-*O*-(*N*-demethylforosaminyl) analog was prepared as shown in Figure 10. This analog was chosen over the natural forosaminyl analog because of the anticipated ease of coupling of a non-basic amide derivative of forosamine, in this case, an *N*-demethyl-*N*-TROC derivative, with the 9-pseudoaglycone. This, indeed, was found to be the case, as the coupling proceeded in good yield (77%). The D-forosamine starting material was obtained by acid hydrolysis of spinosyn A as described previously (*6*). Because the 1-*O*-trichloroacetimidate of the *N*-demethylated forosamine proved highly unstable and thus difficult to isolate, coupling with the pseudoaglycone was effected by way of the 1-*O*-(4-nitrobenzoyl) derivative, which proved to be both easily prepared and quite stable.

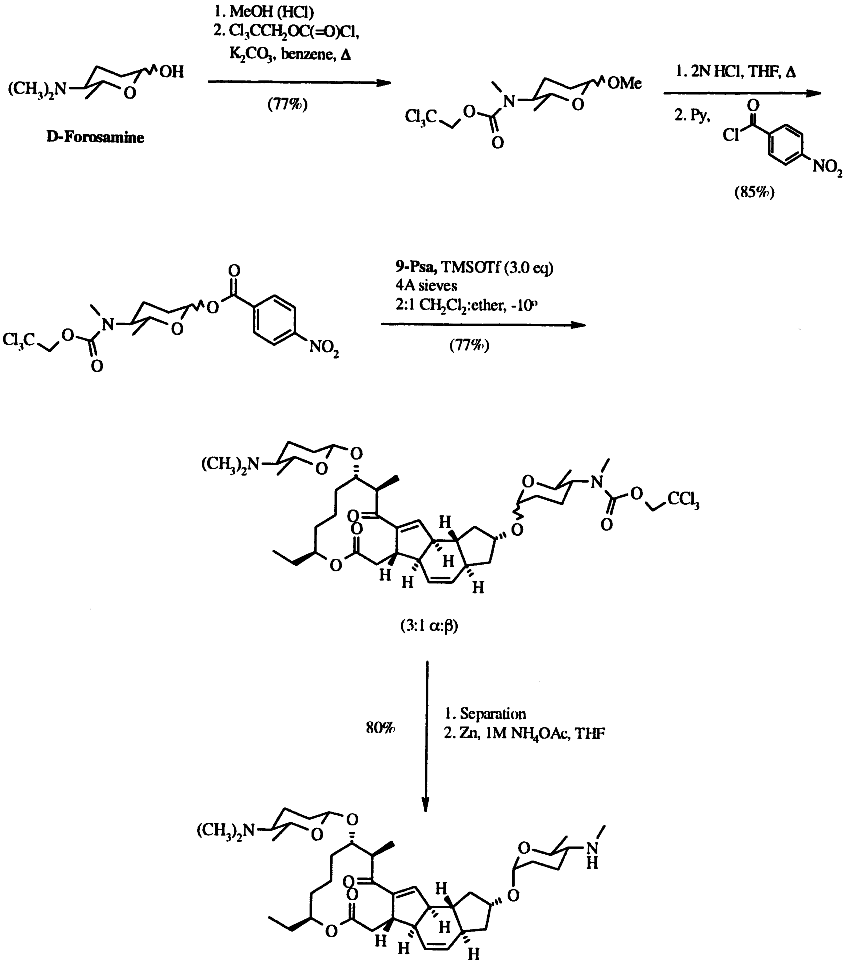
1. MeOH (HCl)
2. Cl3CCH2OC(=O)Cl, K2CO3, benzene, Δ
(77%)
(CH3)2N
OH
O
D-Forosamine
Cl3C
N
OMe
1. 2N HCl, THF, Δ
2. Py,
Cl
NO2
(85%)
9-Psa, TMSOTf (3.0 eq)
4A sieves
2:1 CH2Cl2:ether, -10°
(77%)
CCl3
H
(3:1 α:β)
80%
1. Separation
2. Zn, 1M NH4OAc, THF
N
H

Figure 10

Non-sugar Analogs

The 9-*O*-methoxybenzoates, 9-*O*-methyl and 9-*O*-(2-methoxy)ethyl ether analogs were prepared from the pseudoaglycone in good yields by standard methodologies as outlined in Figure 11.

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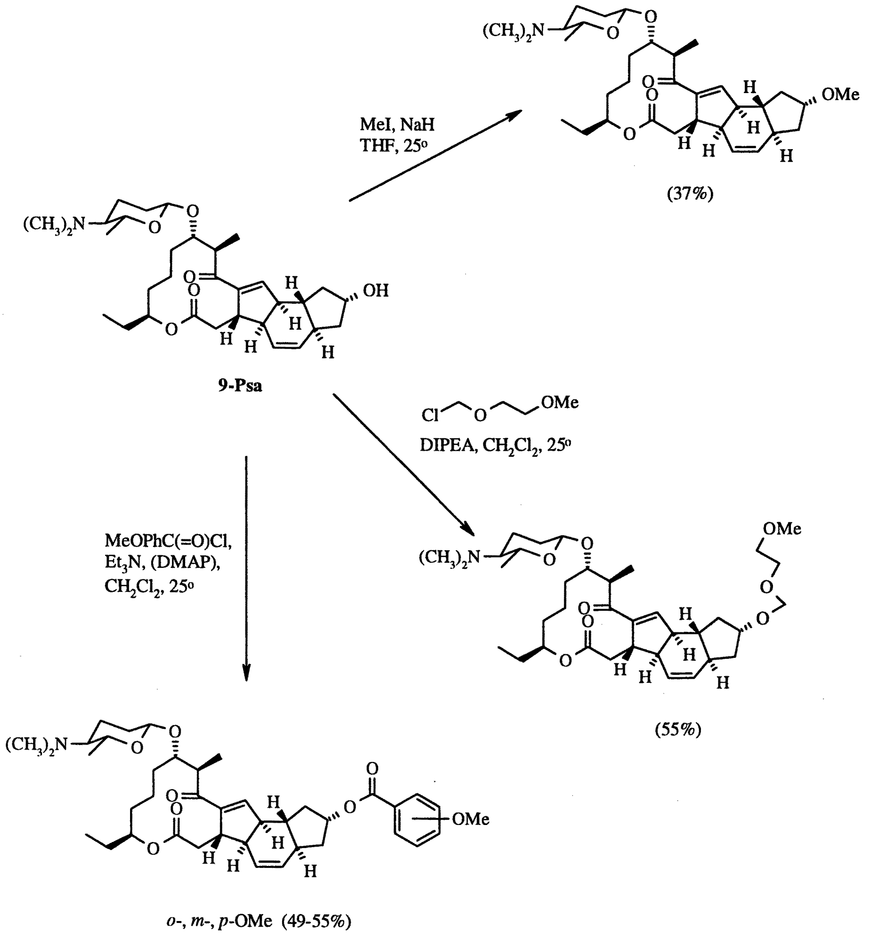
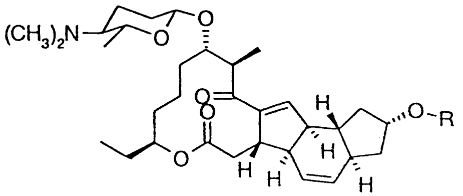

MeI, NaH
THF, 25°
(37%)
9-Psa
Cl⌒O⌒⌒OMe
DIPEA, CH₂Cl₂, 25°
MeOPhC(=O)Cl,
Et₃N, (DMAP),
CH₂Cl₂, 25°
(55%)
o-, m-, p-OMe (49-55%)
(CH₃)₂N
OMe
OH
H

Figure 11. Syntheses of non-sugar analogs

Insect Activities of the Analogs

The LC50 data (in ppm) of the various analogs against tobacco budworm (TBW, neonate 3rd instar larvae) and two-spotted spider mite (TSSM, acute) are shown in Table I. From this data it is quite clearly seen that the ***spinosyns can tolerate very little change about the rhamnose moiety and retain activity***: the D-sugar-, β-anomeric sugar-, furanose sugar-, forosaminyl- and non-sugar analogs were all inactive against both TBW and TSSM. The

Table I. Rhamnose Replacement Analogs



Entry	R	Tobacco Budworm LC50 (ppm)	Two-spotted Spider Mite LC50 (ppm)
1	Tri-*O*-methyl-α-L-rhamnopyranosyl (Spinosyn A)	0.31	0.4
2	Tri-*O*-methyl-α-D-rhamnopyranosyl	> 64	38.9
3	Tri-*O*-methyl-β-D-rhamnopyranosyl	> 64	> 50
4	Tri-*O*-ethyl-α-L-rhamnopyranosyl	0.02	0.4
5	Tri-*O*-ethyl-β-L-rhamnopyranosyl	0.74	
6	Tetra-*O*-methyl-α-L-mannopyranosyl	0.04	
7	Tetra-*O*-methyl-β-L-mannopyranosyl	> 64	
8	Tri-*O*-methyl-α-L-lyxopyranosyl	1.01	1.3
9	Tri-*O*-methyl-β-L-lyxopyranosyl	> 64	> 50
10	Tri-*O*-methyl-α-L-ribofuranosyl	> 64	> 50
11	Tri-*O*-methyl-β-L-ribofuranosyl	> 64	> 50
12	2-Deoxy-3,4-di-*O*-acetyl-α-L-rhamnopyranosyl	23	> 50
13	2-Deoxy-3,4-di-*O*-ethyl-α-L-rhamnopyranosyl	0.12	50
14	2-Deoxy-3,4-di-*O*-propyl-α-L-rhamnopyranosyl	0.24	> 50
15	2-Deoxy-3,4-di-*O*-(2-propyl)-α-L-rhamnopyranosyl	0.82	> 50
16	*N*-Demethyl-α-D-forosaminyl	> 64	
17	*N*-Demethyl-β-D-forosaminyl	> 64	
18	3-*O*-(Tri-*O*-ethyl-α-L-rhamnopyranosyl)-2,4-di-*O*-methyl-α-L-rhamnopyranosyl	> 64	> 50
19	3-*O*-(Tri-*O*-ethyl-β-L-rhamnopyranosyl)-2,4-di-*O*-methyl-α-L-rhamnopyranosyl	9.7	
20	Methyl	> 64	
21	2- Methoxyethoxymethyl	> 64	
22	*p*-Methoxybenzoyl	> 64	
23	*m*-Methoxybenzoyl	> 64	
24	*o*-Methoxybenzoyl	> 64	

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α,α'disacchararide analog (*entry 18*) showed no TBW or TSSM activity, but the α,β' analog (*entry 19*) retained activity against TBW, but was some 30-fold less active. Removal of the 6'-methyl group (L-lyxose analog, *entry 8*) did not significantly affect activity (for TBW: 1.01 vs 0.31), while addition of a methoxyl group to the 6'- methyl group (L-mannose analog, *entry 6*) led to an enhancement of activity of almost an order of magnitude, at least with respect to TBW (0.04 vs 0.31). The 2-deoxy analogs (*entries 13-15*) showed somewhat enhanced TBW activity but essentially no TSSM activity relative to their parents. With regard to the R group on the remaining oxygens of these last analogs, electronegative groups resulted in loss of TBW activity, while relatively small alkyl groups (Me, Et, Pr) showed the highest activity, with Et the best of these (0.12 vs 0.31 for spinosyn A).

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Chapter 26

Design of Scytalone Dehydratase-Inhibiting Rice Blast Fungicides

Gregory S. Basarab[1,4], Douglas B. Jordan[2], Troy C. Gehret[1], Rand S. Schwartz[3], J. Michael Bonman[3], and G. Shawn Smith[3]

[1]DuPont Central Research and Development and [2]DuPont Pharmaceuticals
Company, Experimental Station, Wilmington, DE 19880
[3]Stine-Haskell Research Center, DuPont Agricultural Products,
Newark, DE 19714
[4]Current address: AstraZeneca Research and Development Boston, 35
Gatehouse Drive, Waltham, MA 02145

By targeting the enzyme scytalone dehydratase for inhibitor design, a series of highly efficacious rice blast fungicides were identified. Evaluation for disease control in a series of greenhouse and field assays led to the discovery of an exceptionally potent trifluoro-subtituted cyanoacetamide. Key to the design effort was the recognition that the lipophilicity of the chemistry was generally directly related to inhibitory potency but indirectly related to greenhouse efficacy. The incorporation of fluorine atoms during the design program afforded potent inhibitors and optimized physical-chemical properties important for bioavailability and superior control of rice blast disease.

Scytalone dehydratase (SD) is an enzyme that mediates two reactions in the melanin biosynthetic pathway of various fungi including the agronomically important rice blast pathogen, *Magnaporthe grisea* (*1,2*). Carpropamid (**1**) is an

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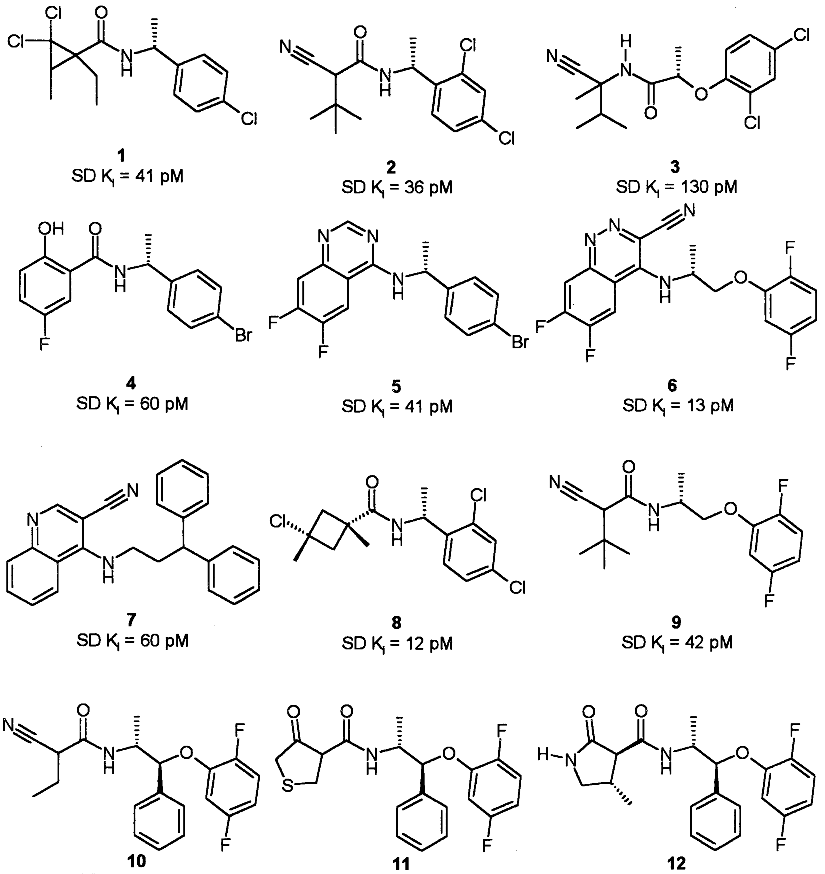

1
SD K_i = 41 pM

2
SD K_i = 36 pM

3
SD K_i = 130 pM

4
SD K_i = 60 pM

5
SD K_i = 41 pM

6
SD K_i = 13 pM

7
SD K_i = 60 pM

8
SD K_i = 12 pM

9
SD K_i = 42 pM

10
SD K_i = 27 pM

11
SD K_i = 14 pM

12
SD K_i = 105 pM

Figure 1. Inhibitors of scytalone dehydratase

SD inhibiting compound that was introduced into the marketplace as a rice blast control agent in 1998 (*3,4*). Dicyclomet (**2**) (*5,6*) and AC 382042 (**3**) (*7*), two other SD inhibitors, have been announced as development candidates for control of the disease. Here we describe the design of novel SD-inhibiting rice blast fungicides leading to the discovery a particularly effective, nonphytotoxic rice blast disease control agent as evaluated in a series of greenhouse and field tests.

A number of other potent SD inhibitors together serve to underscore a level of plasticity of the inhibitor binding pocket. Salicylamide **4** was described in complex with SD in an x-ray crystal structure reported in 1994 (*8*). From the realization that the phenol and carboxamide of **4** form a six-member ring via an intramolecular hydrogen bond, aminoquinazolines such as **5** were derived and demonstrated to inhibit the enzyme (*9,10*). The aminoquinzoline 2-position nitrogen is associated with a crystallographic water molecule in a complex with SD (*10*) leading to the design of cyanocinnolines and cyanoquinolines such as **6** and **7**, respectively, in which the nitrile displaces the water molecule (*11*). Cyclobutane carboxamide **8** was identified from an optimization program that followed a lead discovery in a directed combinatorial synthetic library (*12,13*). Cyanoacetamide **9** was designed with the longer chain N-phenoxypropyl substituent being accommodated by the space defined by the N-bromophenethyl substituent of **2** modeled in the SD binding pocket (*14*). The N-phenoxypropyl group from **9** was further modified to **10** with a stereospecifically positioned phenyl group accommodated by a conformational realignment of the enzyme (*15*). The ketone carbonyl of **11** provides a hydrogen bonding pharmacophore with an active site asparagine residue to account for the high SD inhibitory potency (*16*). The varlerolactam of **12** displays the carboxamide towards this same asparagine for the formation of two hydrogen bonds (*16*).

The promiscuity of the enzyme inhibitor binding pocket is well evident by the structural diversity inherent in the compounds of Figure 1; however, potency against SD is not necessarily commensurate with *in vivo* activity. The control of rice blast disease in greenhouse evaluations by **4**, **5**, **6**, **7** and **11** (Figure 1) was considerably less than the control displayed by the **1**, **2** and **3** which are being commercialized. The reasons for this are varied. The fungus likely detoxifies salicylamide **4** and tetrahydrothiophenone **11** via glucuronidation (*17*). Due to the poor capability to move systemically in the plant, sufficient concentrations of **5**, **6** and **7** do not accumulate on the rice leaf surface to arrest fungal infection. Analogue synthesis around **8**, **9** and **12**, all efficacious for disease control, has been reported. We report here further optimization synthesis and biological evaluation around **9** by modification of the *t*-butyl substituent.

Chemistry

A crystal structure of SD in complex with **9** was determined to 1.9 Å resolution (*14*) using the published (3STD (*10*)) SD crystal structure complex with **4** as the initial model. A salient feature from the model of **9** in the SD binding pocket is the opportunity to expand the size of two of the methyl groups on the *t*-butyl substituent. Figures 2A and 2B show the modeled replacement of the two methyl groups with a vinyl group in a Connolly surface generated for the enzyme binding pocket. In the first case, the vinyl group is positioned close to Ser129, a residue implicated in catalysis via the formation of a hydrogen bond with substrate scytalone (*18*). In the second case, the vinyl group points towards Phe53, a conformationally mobile residue as indicated from comparisons of multiple SD crystal structures (*10,15*). Additionally one of the *t*-butyl methyl groups can be replaced with an acetylene that extends into the binding pocket

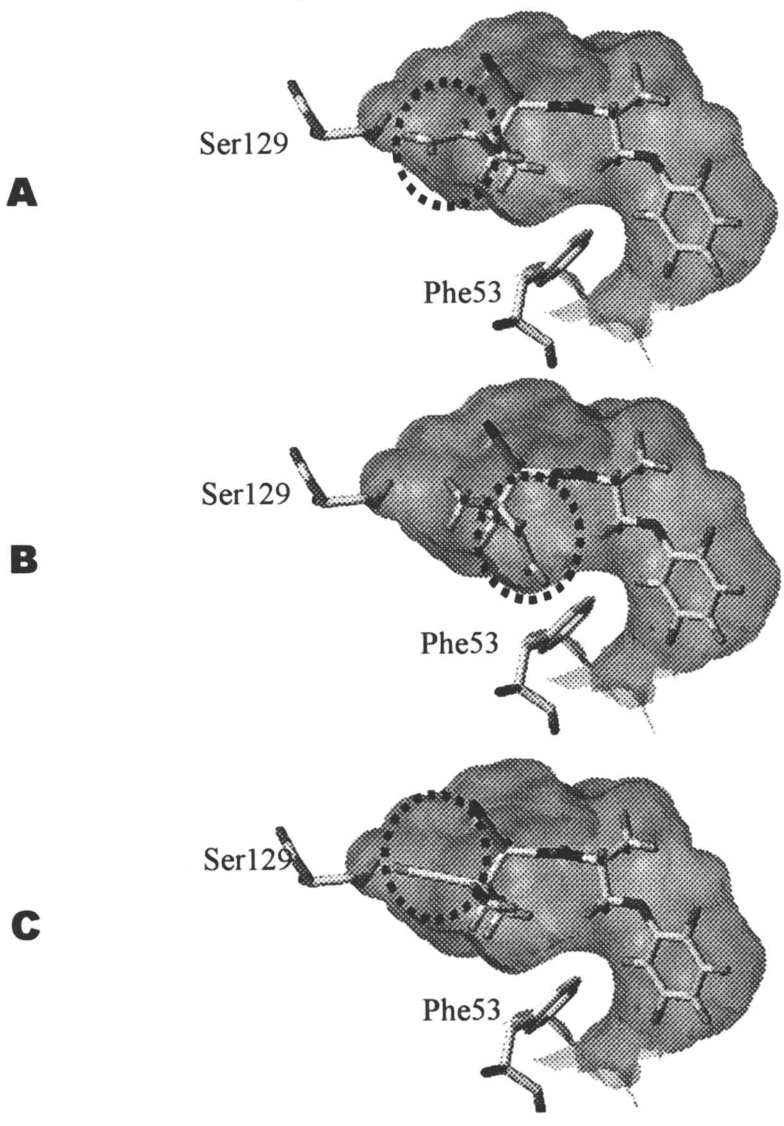


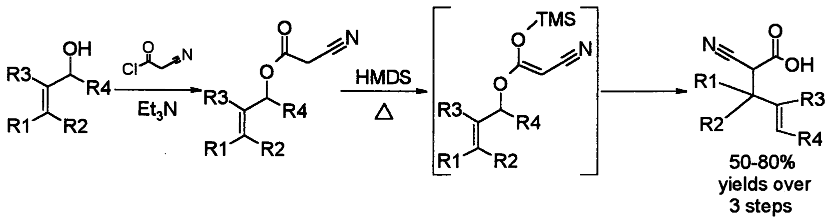
*Figure 2. **A** and **B** depict two orientations of the vinyl substituent of **14** (towards Ser129 and Phe53, respectively) within a Connolly surface of the buried SD binding pocket. **C** depicts the orientation of the acetylene substituent of **24** towards Ser129 within the Connolly surface.*

bordered by Ser129 (Fig 2C). With these models in mind, we set out to synthesize various vinyl and acetylenyl variants of tertiary alkyl substituents attached α to cyanoacetamides. In particular, we were intrigued by the influence that fluorine substitution might have on expression of activity of these vinyl and acetylenyl cyanoacetic acids.

Synthesis of vinyl cyanoacetamides

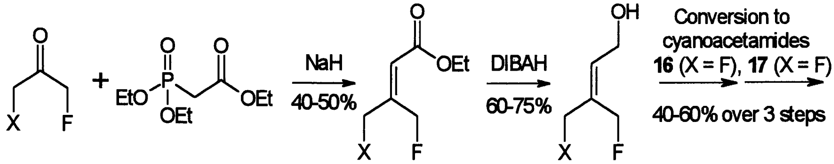
The synthesis of analogues with the vinyl substituent proceeded, for the most part, through an Ireland-Claisen rearrangement. The allyl alcohol for the preparation of **14** of Table 1 (Scheme 1, R1 = R2 = CH_3, R3 = R4 = H) is available commercially, and its esterification with cyanoacetyl chloride followed by heating in hexamethyldisilazane cleanly affords the cyanoacetic acid after mild acid hydrolysis of the trimethylsilyl ester. Similarly, **15** is prepared when R1 = CH_3, R2 = C_2H_5, and R3 = R4 = H.

Scheme 1

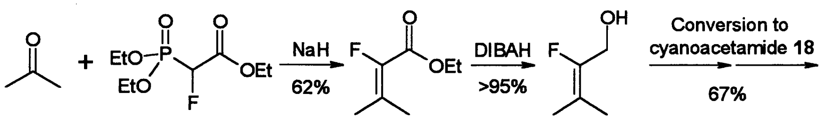

OH
R3
R4
R1
R2
Cl
O
N
Et3N
O
O
N
R3
R4
R1
R2
HMDS
Δ
TMS
O
O
N
R3
R4
R1
R2
N
O
OH
R1
R2
R3
R4
50-80%
yields over
3 steps

The sequence of Scheme 1 was particularly useful for the synthesis of fluorinated analogues **16**, **17** and **18**. To this end, Horner-Emmons olefination with mono and difluoroacetone followed by reduction of the resultant esters to the alcohols afforded fluoromethyl derivatives (*19,20*), which were readily incorporated into the final products (Scheme 2). A similar sequence with an α-fluorophosphonoacetate and acetone afforded the vinyl fluoride which, on acylation with cyanoacetyl chloride and rearrangement affixes the fluorine atom on the internal vinyl carbon (Scheme 3).

Scheme 2

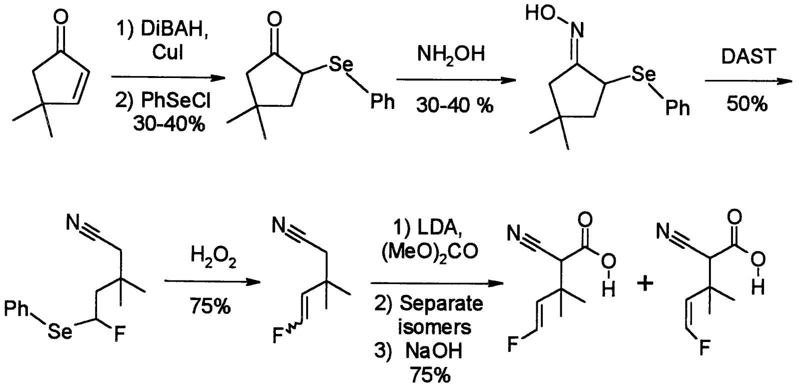

O
X
F
+
O
O
EtO
P
OEt
OEt
NaH
40-50%
O
OEt
X
F
DIBAH
60-75%
OH
X
F
Conversion to
cyanoacetamides
16 (X = F), 17 (X = F)
40-60% over 3 steps

Scheme 3


O
+
O
O
EtO
P
EtO
OEt
F
NaH
62%
F
O
OEt
DIBAH
>95%
F
OH
Conversion to
cyanoacetamide 18
67%

Since the R4 substituent of Scheme 1 cannot be halogen due to the instability of the intermediate allylic alcohol, an alternative route to incorporate a terminal vinyl fluoride was devised (Scheme 4). Cuprate catalyzed conjugate reduction of the dimethylcyclopentenone followed by selenation and conversion to the oxime set the stage for a diethylaminosulfur trifluoride (DAST) mediated Beckmann fragmentation. A similar fragmentation has been reported for α-sulfenyl oximes (*21*). The fragmentation generates the nitrile functionality and appropriately positions the fluorine atom while subsequent selenoxide elimination generates the olefin. The 3:2 mixture of *trans* to *cis* olefin isomers obtained could be separated after carboxylation α to the nitrile. The isolated cyanoacetic esters were individually hydrolyzed to the acids and converted to the desired carboxamides **19** and **20**.

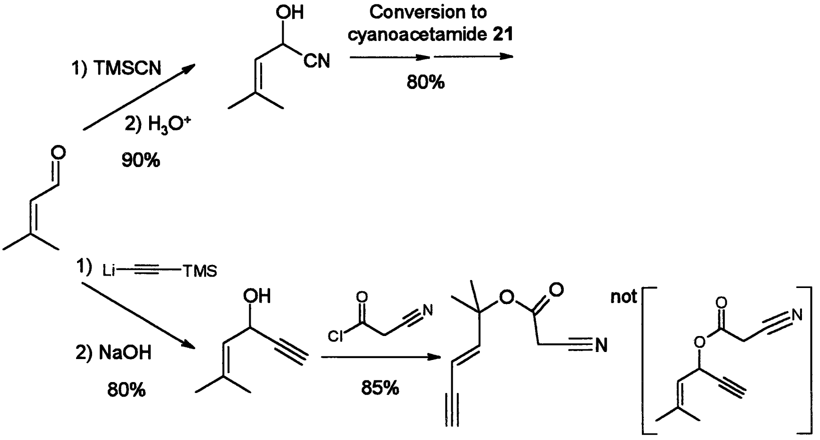
Scheme 4



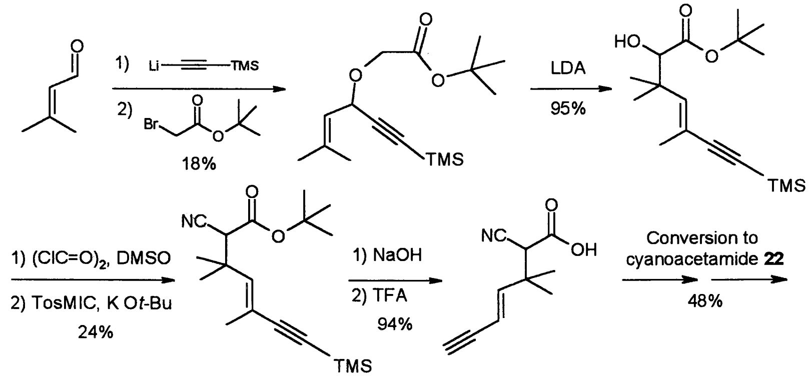
Allowing R4 of Scheme 1 to be a nitrile was achieved through synthesis of the trimethylsilyl cyanohydrin derived from 3-methyl butenal (*22*). Subsequent acylation and rearrangement affords predominately the *E*-isomer. Incorporation of an acetylene unit via similar chemistry failed as acylation with cyanoacetyl chloride led to a premature oxygen to oxygen [3,3]-sigmatropic rearrangement (see Scheme 5) promoted by the carbocation stabilizing acetylene.

Due to this limitation, an alternative route to the enyne via a [2,3]-sigmatropic rearrangement rather than a [3,3]-sigmatropic rearrangement was devised (Scheme 6). Lithium trimethlylsilyl acetylide was added to 3-methylbutanal followed by *in situ* alkylation of the resultant alkoxide with *t*-butyl bromoacetate. A lithium diisopropylamide mediated Wittig rearrangement followed by a Swern oxidation affords a ketone, which allows for toluenemethyl isocyanate conversion to the nitrile. This sets in place all the necessary functionalities for conversion to the final product, which is produced by removal of the trimethylsilyl and *t*-butyl protecting groups and conversion to the amide.

Scheme 5


OH
CN
Conversion to cyanoacetamide 21
80%
1) TMSCN
2) H_3O^+
90%
O
1) Li—≡—TMS
2) NaOH
80%
OH
O
Cl
N
85%
O
O
N
not
O
O
N

Scheme 6

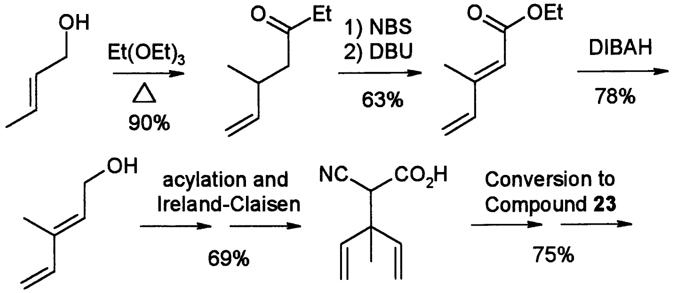

O
1) Li—≡—TMS
2) Br
O
O
18%
O
O
O
TMS
LDA
95%
HO
O
O
TMS
1) (ClC=O)$_2$, DMSO
2) TosMIC, K O*t*-Bu
24%
NC
O
O
TMS
1) NaOH
2) TFA
94%
NC
O
OH
Conversion to cyanoacetamide 22
48%

As mentioned earlier from the binding model of inhibitors to SD, either of two of the *t*-butyl methyl groups could be replaced with a two-carbon vinyl group. It follows that a bis-vinyl derivative would be tolerated by the enzyme. Hence, ortho ester mediated Claisen rearrangement of 2-buten-1-ol followed by a net dehydrogenation and a reduction of the ester to the alcohol affords the appropriate synthon (*23*) for the Ireland-Claisen route to **23** (Scheme 7).

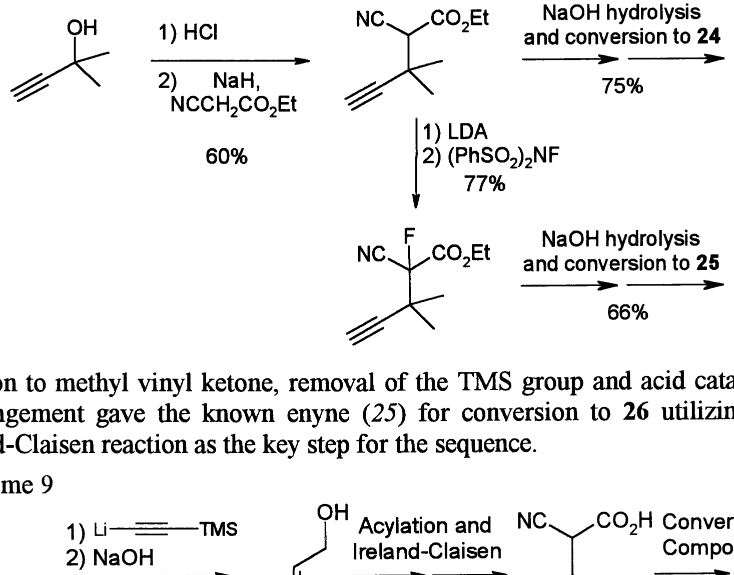
The acetylene containing cyanoacetic ester for conversion to **24** is known from the literature (*24*) (Scheme 8). The intermediate ester was fluorinated at the α-position using a bis-sulfonamide electrophilic fluorine source. Conversion to **25** was achieved by hydrolysis and standard conditions for amide coupling.

Finally, an acetylenyl and vinyl hybrid was synthesized since replacing one *t*-butyl methyl group of **9** with an acetylene and another with a vinyl group is well accommodated by the SD binding model. Lithium trimethylsilylacetylide

Scheme 7

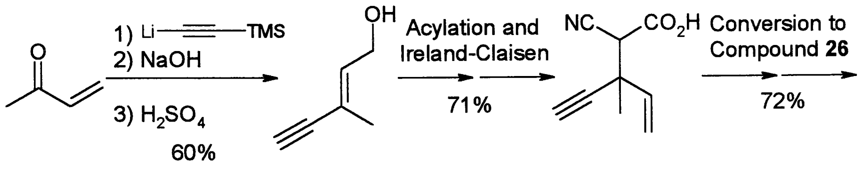

OH
Et(OEt)$_3$
Δ
90%
O
Et
1) NBS
2) DBU
63%
O
OEt
DIBAH
78%
OH
acylation and
Ireland-Claisen
69%
NC
CO$_2$H
Conversion to
Compound **23**
75%

Scheme 8


OH
1) HCl
2) NaH,
NCCH$_2$CO$_2$Et
60%
NC
CO$_2$Et
NaOH hydrolysis
and conversion to **24**
75%
1) LDA
2) (PhSO$_2$)$_2$NF
77%
F
NC
CO$_2$Et
NaOH hydrolysis
and conversion to **25**
66%

addition to methyl vinyl ketone, removal of the TMS group and acid catalyzed rearrangement gave the known enyne (*25*) for conversion to **26** utilizing the Ireland-Claisen reaction as the key step for the sequence.

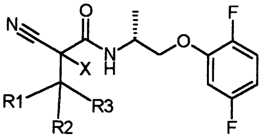
Scheme 9


O
1) Li———TMS
2) NaOH
3) H$_2$SO$_4$
60%
OH
Acylation and
Ireland-Claisen
71%
NC
CO$_2$H
Conversion to
Compound **26**
72%

Biological Evaluation

All the compounds of this paper were evaluated for inhibitory potency against SD and for the ability to control rice blast disease in two different greenhouse assays, one with a foliar application and a second with soil application (Table 1). The SD inhibition assay spectrophotometrically follows

Table 1. SD Inhibition and Rice Blast Disease control



Cmpd #	X	R1	R2	R3	SD K_i (pM)	Foliar ED_{90} (ppm)	Systemic ED_{90} (ppm)
9	H	CH_3	CH_3	CH_3	42	6.2	0.7
13	H	CH_3	CH_3	H	270	12.5	2.1
14	H	CH_3	CH_3	$CH=CH_2$	24	0.8	0.6
15	H	CH_3	C_2H_5	$CH=CH_2$	31	6.2	1.6
16	H	CH_3	CH_2F	$CH=CH_2$	24	0.8	0.1
17	H	CH_2F	CH_2F	$CH=CH_2$	63	25	7.5
18	H	CH_3	CH_3	$CF=CH_2$	27	0.4	0.2
19	H	CH_3	CH_3	$CH=CHF$ (*trans*)	29	0.8	0.3
20	H	CH_3	CH_3	$CH=CHF$ (*cis*)	63	1.6	0.2
21	H	CH_3	CH_3	$CH=CHCN$ (*trans*)	59	100	>10
22	H	CH_3	CH_3	$CH=CHC\equiv CH$ (*trans*)	26	50	7.5
23	H	CH_3	$CH=CH_2$	$CH=CH_2$	23	0.8	1.0
24	H	CH_3	CH_3	$C\equiv CH$	63	6.2	1.9
25	F	CH_3	CH_3	$C\equiv CH$	210	>200	>10
26	H	CH_3	$CH=CH_2$	$C\equiv CH$	41	6.2	1.7
1			-		40	3.1	2.2

the conversion of substrate to product at multiple dosages of compound to determine K_i (*11*). The foliar greenhouse assay involves application of compound to rice seedlings preceding inoculation with the rice blast pathogen at multiple dosages to determine an ED_{90} or concentration necessary to eradicate 90% of the disease (*26*). The soil application also reports an ED_{90} and measures the capability of a compound to partition away from the soil, progress into the roots and move systemically through the rice plant to control disease (*13*). Systemic movement through the rice plant is deemed crucial for control of disease via the preferred farming practices of applying fungicides either to the soil in seedling containing nursery boxes or to the water of flooded rice paddies. Compounds that excelled in the soil application were evaluated in advanced greenhouse assays designed to mimic the nursery box and paddy applications. The SD inhibition assay, which uses enzyme from the target organism, offers a rationalization of much of the data generated in the greenhouse assays and focuses design efforts into addressing those properties that are necessary for expression of greenhouse activity.

Structure-activity correlations

2,5-Difluoro substitution on the phenyl ring was maintained as a constant for the analogues presented in Table 1. Other substituents and other substitution patterns were synthesized with most of the cyanoacetamides of Table 1, but invariably greenhouse fungicidal activity declined (*14*). Chlorine atoms could be tolerated in place of fluorine in either the 2- or 5-position relative to SD binding potency, but the net increase in hydrophobicity compromised systemic movement in the rice plant and decreased the ability to control disease in the greenhouse assays. The synthesis of the chiral *R*-configured amine common to all the carboxamides of Table 1 has been described previously (*14*).

In coupling the chiral amine with racemic cyanoacetic acids, mixtures of two or four diastereomers are obtained depending on the precursor cyanoacetic acids having one or two chiral centers. When the cyanoacetic acids contain one center of chirality, the two resultant diastereomers can be separated by chromatography. SD inhibitory activity resides with the *R,R* absolute stereochemistry for the resultant cyanoacetamides (*14*). During the course of greenhouse assays, there is significant racemization of the *S,R* configured cyanoacetamides such that they express disease control. Hence, the compounds of Table 1 were assayed as diastereomeric mixtures. The synthesis and bioactivity of **9** (*14*) and **13** (*15*) have been described previously; their biological activities are included in Table 1 for structure-activity comparisons.

Having a tertiary carbon atom attached to the cyanoacetic moiety is optimal for activity. The binding potency to SD on removal of one methyl group from the *t*-butyl substituent is diminished nearly 7-fold. Commensurately, greenhouse activity is compromised (compare **9** with **13**, Table 1). The binding site surrounding the *t*-butyl group of **9** is quite hydrophobic, and occupying the site to the greatest extent possible with a sterically allowed hydrophobic functionality increases binding potency due to the inhibitor favorably partitioning away from the water environment. Maintaining the tertiary carbon while replacing one CH_3 of the *t*-butyl group with a vinyl group (going from Compound **9** to **14**) increased SD inhibitory potency from a K_i = 42 pM to a K_i = 24 pM. Gratifyingly, the potency against rice blast disease in both the foliar and systemic greenhouse assays also increased outperforming carpropamid (Compound **1**). This data validates the design thesis in that the vinyl group was well accommodated by the SD binding model. As mentioned, care must be taken in the design of inhibitors to avoid increasing binding potency only by adding lipophilicity as doing so impairs systemic movement in the rice plant and expression of disease control. This is born out for **15** which has a K_i = 31 pM versus SD but does not proportionately control disease. The additional methyl group of **15** relative to **14** crosses a threshold in lipophilicity diminishing systemic movement in the plant.

Compound **16** (K_i = 24 pM) with the mono-fluoromethyl group exists as a mixture of four diastereomers and excelled in both the foliar and systemic greenhouse assays. It is likely that one of the diastereomers of **16** is primarily responsible for the activity, as the bis-fluoromethyl analogue **17** without the asymmetry at the tertiary carbon is 2-3 times less potent versus SD. However, the greenhouse activity of **17** was even less than what would have been expected given the K_i and the presumed greater degree of hydrophilicity relative to **14** and **16**. Fluorine substitution on the cyanoacetamide alkyl substituent increases the acidity of the proton between the nitrile and carboxamide leading to a measure of chemical and metabolic instability, which likely accounts for the lower efficacy in the greenhouse assays. Compound **17** is particularly sensitive to mild base treatment cyclizing to the cyclopropane via enolization and displacement of a fluorine atom, and care must be taken during its preparation to avoid the use of even a mild base in excess.

As with fluorine substitution on methyl groups, fluorine substitution on the vinyl group generates particularly potent SD inhibitors and rice blast fungicides. Compounds **18**, **19** and **20** give SD K_i's of 27, 29 and 63 pM, respectively, while maintaining excellent foliar and systemic greenhouse activities. Clearly, these compounds maintain a balance of metabolic stability and physical properties for systemic movement through the rice plant that elicits the superior expression of disease control. More advanced greenhouse assays were carried out on these and other of the better performing compounds to select candidates for evaluation in outdoor field trials. However, it was recognized that **19** and **20** suffer from the impracticality of the synthetic preparation outlined in Scheme 4 where yields are low, and reagents are prohibitively expensive for scale-up. No other efficient route **19** or **20** could be envisioned, and therefore **18** generated higher interest.

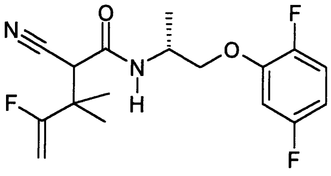
The remaining compounds of Table 1 that incorporate a vinyl group are quite potent SD inhibitors, though the expression of greenhouse efficacy is variable. The bis-vinyl analogue **23** (K_i = 23 pM) validates the SD binding model that allows incorporation of the two vinyl substituents. Correspondingly, **23** performed quite well in the foliar and systemic greenhouse assays. When one of the vinyl groups of **23** is replaced with an acetylene (Compound **26**), there is a 2-fold reduction in SD inhibitory potency and systemic greenhouse efficacy and an 8-fold reduction in foliar greenhouse efficacy. Enyne **22** also performs less well in the greenhouse than what might be predicted from K_i. Overall, the acetylene functionality in this and other analogues (see below) adversely affects performance in greenhouse assays relative to what might be expected from inhibitory potency suggesting the functionality serves as a handle for metabolism. Substitution of a nitrile on the vinyl group (Compound **21**, K_i = 59) is tolerated for SD inhibition, but greenhouse activity is notably compromised. The acrylonitrile functionality of **21** likely provides a handle for metabolic detoxification by the plant or fungus.

Having an acetylene in place of the vinyl group is well tolerated by the SD binding model and accordingly confers a K_i = 63 pM (Compound **24**). By placing a fluorine atom between the nitrile and carboxamide (affording Compound **25**), the resultant diastereomers could not racemize allowing for isolation of the active diastereomer without epimerization *in vivo*. It was anticipated from the SD binding model that fluorination between the nitrile and carboxamide would raise K_i as the fluorine atom would occupy a position adjacent to a crystallographic water molecule that is associated in a hydrogen bonding network with the inhibitor NH and two enzyme histidine residues. Indeed, this is the case as the fluorine atom decreases binding potency by over 3-fold. More importantly, the electronegative fluorine α to the carboxamide and nitrile reduces the electronegativity of the system significantly increasing the hydrophilicity. Not unexpectedly, **25** did not show control of rice blast disease at any of the tested rates underscoring the importance of physical properties for the expression of greenhouse activity. To accentuate this point, compare **25** to **13**: the latter has a higher K_i, but is considerably more hydrophilic and thereby records control of the rice blast fungus in the greenhouse assays.

Field evaluations

Those compounds in Table 1 that control disease at rates less than or equal to 3 ppm were further evaluated in advanced greenhouse assays that attempt to mimic paddy and nursery box application of compound. Five compounds (**9**, **14**, **16**, **18**, and **19**) displayed the highest activity in the aggregate of advanced greenhouse assays with **18** and **19** emerging as the most active. As mentioned, synthetic limitations prevented the consideration of testing **19** in outdoor field tests. Compound **16** with four diastereomers was also eliminated from consideration, as it offered no biological efficacy advantage over the other four compounds. Field evaluations were carried out in Japan with **9**, **14**, and **18**, with the order of efficacy being **18** > **14** > **9**, the latter performing about equal to carpropamid. Compounds **9**, **14** and **18** did not display phytotoxicity to the rice plant, aquatic toxicity (to daphnia, carp or fat-head minnows), mammalian toxicity (mice or rats) or bacterial mutagenicity in an Ames test.

In summary, greenhouse systemic and foliar evaluations were carried out in conjunction with an SD inhibition determination to optimize a series of cyanoacetamides for rice blast disease control. It was important to understand inherent activity (expressed as K_i) against the enzyme target to dissect, in part, the various contributions that play roles in the expression of greenhouse and outdoor field activity. Lipophilicity was shown to be a major determinant for the expression of activity. Fluorination at the appropriate positions of the cyanoacetamide generally improved physical properties relevant to systemic movement in the rice plant. It was also important to have sufficient metabolic stability to allow a given compound to control disease for an anticipated two or more months in the field. Compound **18** displayed the highest activity in field evaluations in Japan. That it was optimized from considerations of target-site inhibition mitigated toxicity to off-target organisms resulting in a remarkably safe rice blast fungicide.



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Chapter 27

Calvatic Acid and Its Analogues as Agricultural Fungicides

Andrew C. G. Gray[1], Gottfried Kremp[2], Thomas W. Naisby[1], Thomas Petry[2], Werner Simon[2], Jacki Wilkin[1], and William W. Wood[3],*

[1]Shell Research Ltd., Sittingbourne, Kent ME9 8AG, United Kingdom
[2]Cyanamid Forschung Schwabenheim, Zur Propstei, D–55270, Germany
[3]BASF Agro Research Center, Quakerbridge and Clarksville Road, Princeton, NJ 08543 (formerly Cyanamid Agricultural Research Center)

Azoxycyanides belonging to two distinct structural groups were prepared and evaluated as potential agricultural fungicides. A benzanilide derivative was found to be the most effective of the direct analogues of calvatic acid, while a coumarin and two benzo-ketals were found to be the optimum compounds in the bicyclic series. Field trial results showed that these compounds were highly active against commercially important diseases, but did not attain the levels of activity necessary for commercial development.

One of the more unusual natural products, calvatic acid is a yellow powder isolated from several different *Calvatia* and *Lycoperdon spp.* of puffball mushroom.[1] The antibacterial activity of the compound, and of several close analogues isolated at the same time, was noted by the original authors, who also reported some antimycotic activity for these compounds. There has also been a considerable volume of work published on the use of azoxycyanide analogues for the control of cancer.[2] Our interest in the area was sparked by an

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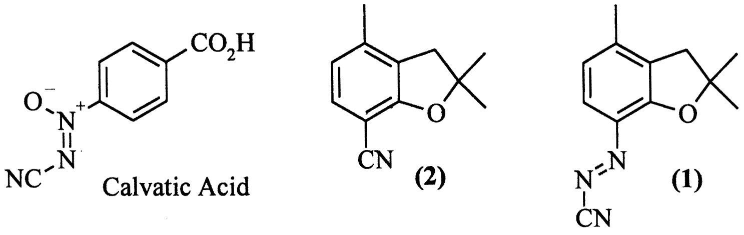
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

observation of the antifungal activity of an azocyanide (I) (see Figure 1),[3] formed as as by-product in the preparation of the cyanide (**2**). This compound showed control of *Plasmopara viticola* equivalent to that of mancozeb, but was too unstable to use as an agricultural product. The corresponding azoxycyanide also showed good activity and was, as expected, considerably more stable.



Calvatic Acid **(2)** **(1)**

Figure 1: Calvatic acid and lead analogues

Although the project arising from these observations was driven by biological results, rather than by structural considerations, the final outcome may be conveniently divided into two sections. In the first of these, direct analogues of calvatic acid will be reviewed, while in the second bicyclic derivatives, based on (**1**) will be considered. The chemistry used to prepare all of these targets has been described elsewhere.[4]

Analogues of Calvatic Acid

When screened against a variety of agriculturally important diseases, calvatic acid itself showed remarkably little activity, giving only partial control of two diseases in prophylactic tests and of one each in the therapeutic and *in vitro* tests (see Table 1). The simple esters of the acid gave better control, particularly the *tert*-butyl and phenyl esters. Although the activity of the *tert*-butyl analogue fell away sharply at lower doses, the phenyl ester did show consistent control of *P. viticola* down to 30 ppm. Unfortunately this compound did not have a sufficiently broad spectrum of activity to warrant further evaluation.

This was not the case for the benzamides and benzene sulphonamides (Table 1). Both the unsubstituted and the phenyl sulphonamides showed activity against *P. viticola* and some *in vitro* activity, but more significantly, the benzamide and benzanilide derivatives showed broad spectrum prophylactic

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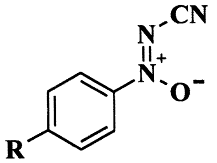
fungicidal activity against all three species in the test. These two analogues were evaluated at lower doses (Table 2), showing that the benzanilide was slightly more potent than the benzamide. In addition, the benzanilide showed activity against *Phytophora infestans*, whereas the benzamide did not. A variety of N-alkyl benzamide derivatives were prepared, to determine whether substitution at nitrogen was all that was required to give the enhanced activity seen with the benzanilide analogue, however it was found that these compounds were significantly less active than either the benzamide or the benzanilide (see Table 3). Those compounds which did show activity at the high dose were evaluated at lower doses and found to be, essentially, inactive.

Table 1: Fungicidal Activity of Calvatic Acid, Esters, Amides and Sulphonamides



	Prophylactic				*Therapeutic*						*In Vitro*	
R	*Pvp*	*Bcp*	*As*		*Ln*	*Eg*	*Pr*	*Po*	*Pva*		*Ph*	*Fs*
CO_2H	1	0	1		0	0	0	0	1		0	1
CO_2Et	0	0	0		0	0	0	0	0		2	2
CO_2Me	0	0	0		2	1	2	0	0		2	2
CO_2tBu	2	0	2		0	2	2	0	1		2	1
CO_2Ph	2	0	0		0	0	0	0	0		0	0
$CO_2C_{12}H_{25}$	0	0	0		0	0	0	0	0		0	0
$CONH_2$	2	2	2		0	0	0	0	0		2	2
SO_2NH_2	2	0	1		1	0	1	0	0		2	2
$CONHPh$	2	2	2		0	0	0	0	0		0	0
SO_2NHPh	2	0	1		0	0	1	0	0		1	2

Compounds screened at 1000 ppm; Scoring system: 2 = complete control, 1 = partial control, 0 = no control

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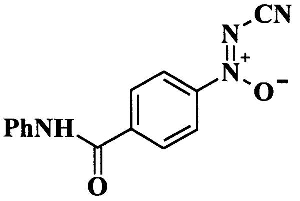
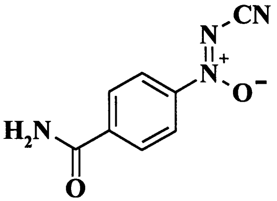
Table 2: Comparison of Fungicidal Activity of Benzanilide and Benzamide Azoxycyanides

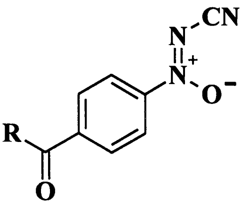




	Benzanilide					*Benzamide*		
Dose (ppm)	As	Bc	Pv	Pi		As	Bc	Pv
300	8.3	8.7	9.0	8.7		7.7	6.3	8.9
100	7.7	7.7	9.0	9.0		2.8	5.0	9
30	4.3	6.0	9.0	5.0		0.0	4.7	7.8

Scoring system: 0-9 scale, 9 = complete control

Table 3: Fungicidal Activity of Benzamide Derivatives

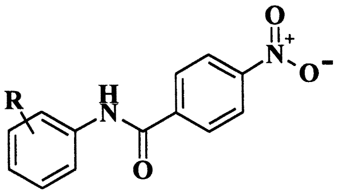


R	*Pvp*	*Bcp*	*As*		*Ln*	*Eg*	*Pr*	*Po*	*Pva*		*Ph*	*Fs*
NH_2	2	2	2				0	0	1		2	2
NMe_2	1	0	0		1	0	0	0	0		2	2
NEt_2	1	0	1		0	0	0	0	1		2	2
NHMe	0	0	0		0	0	0	0	0		2	2
NHnHex	0	0	0		0	0	0	0	0		1	1
$NHnC_{12}H_{25}$	1	0	0		0	0	0	0	0		0	2
NHcPent	0	2	0		0	0	1	0	0		0	1
NHcHex	2	0	1		0	0	0	0	1		1	1
NHcHept	0	2	0		0	0	0	0	0		2	0
$NHCH_2cHex$	0	2	0		0	0	2	0	0		0	1

Compounds screened at 1000 ppm; Scoring system: 2 = complete control, 1 = partial control, 0 = no control

Finally, in this series, the effect of substitution on the anilide ring was evaluated. Some 50+ analogues were prepared in this series, of which a selection of the more active analogues are shown in Table 4. As can be seen from this data, substitution on the anilide ring generally led to retention of fungicidal activity, but no clear trends were observed in either the position of substitution or in the nature of the substituting group. From the data shown below, there is a slight indication that *ortho*-substitution is less favoured, but the data did not convincingly suggest any advantage in substituting the anilide ring. Indeed, in terms of cost-performance, the simple unsubstituted anilide appeared to be the optimum analogue in this particular series.

Table 4: Fungicidal Activity of Substituted Benzanilide Azoxycyanides *vs* *Plasmopara Viticola*



	Dose (ppm)					*Dose (ppm)*		
R	*300*	*100*	*30*		*R*	*300*	*100*	*30*
H	8.0	8.7	6.0		*o-Me*	7.3	5.3	6.0
o-Cl	7.3	8.0	3.3		*m-Me*	8.7	7.7	8.0
m-Cl	9.0	8.6	8.6		*p-Me*	9.0	9.0	7.7
p-Cl	6.4	9.0	9.0		*o-Me*	8.0	9.0	4.3
o-CF$_3$	8.0	6.0	6.3		*m-Me*	9.0	7.0	6.0
m-CF$_3$	7.7	8.7	4.0		*p-Me*	8.0	8.7	6.0
p-CF$_3$	8.0	8.7	4.0					

Scoring system: 0-9 scale, 9 = complete control

Bicyclic Azoxycyanides

As discussed above, the original lead dihydrobenzofuran azocyanide gave good control of *P. viticola*, but was too unstable to be of value as a potential product. The corresponding azoxycyanide (Table 5) was much more stable

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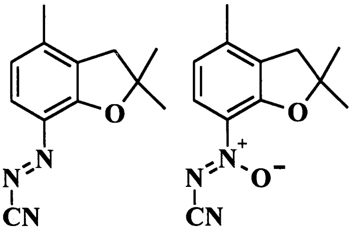
and appeared to be slightly more active as a fungicide than the azo-derivative. In the light of these results a study of bicyclic azoxycyanide derivatives was initiated, designed to look at substitution patterns on both rings, different ring sizes on the furan ring and other related structural types.

A group of substituted dihydrobenzofuran analogues were prepared, many of which gave prophylactic activity against diseases of broad-leaf crops (see Table 6 for selected examples). However none of these analogues gave improved activity over the 4-methyl derivative. Benzofurans were also examined and found to have broad spectrum activity – in particular the 2-methyl analogue showed activity against *P. viticola, A. solani* and several other diseases (Table 7). Interestingly, it was found that moving the azoxycyanide moiety to other positions on the aryl ring dramatically reduced activity, suggesting that the spatial relationship between the ring oxygen and the azoxycyanide may be important in the benzofuran series, however this relationship did not repeat in other series of bicyclic analogues. Expanding the furan ring, to form either a benzopyran or a dihydrobenzopyran, generally led to a reduction in biological potency. In addition, the structure-relationships observed on the aryl ring in this series did not correspond to those found for the benzofuran derivatives.

A variety of azoxycyanides based on alternative bicyclic rings systems were also examined for fungicidal activity. Of these, one of the most effective was a coumarin derivative, carrying the azoxycyanide in the 6-position. This result

Table 5: Dihydrobenzofuran azo- and azoxy- cyanides *vs P. viticola* (Prophylactic)



Dose (ppm)	*Azocyanide*	*Azoxycyanide*
1000	9.0	9.0
300	7.0	9.0
100	4.3	7.1
30	-	3.0

Scoring system: 0-9 scale, 9 = complete control

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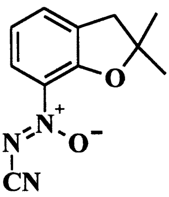
Table 6: Activity of some substituted dihydrobenzofuran azoxycyanides *vs* *P. viticola* (Prophylactic)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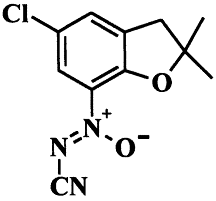
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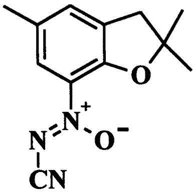
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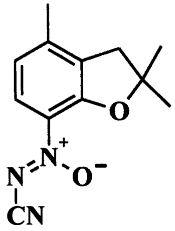
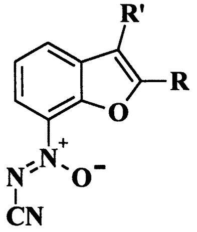

4

Dose (ppm)	*Score (0-9)*			
	1	*2*	*3*	*4*
1000	7.0	9.0	9.0	9.0
300	-	2.0	-	9.0
100	-	2.7	1.7	7.1
30	-	0.6	0.0	3.0

Scoring system: 0-9 scale, 9 = complete control

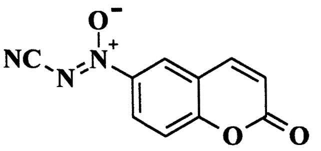
Table 7: Activity of Benzofuran azoxycyanides *vs* *P. viticola* (Prophylactic)



	R=Me, R'=H		*R=R'=Me*		*R=Et, R'=H*	
Dose (ppm)	*Pv*	*As*	*Pv*	*As*	*Pv*	*As*
1000	9.0	9.0	9.0	7.7	0	2.2
300	9.0	6.4	5.9	0	-	1.1
100	8.0	3.9	5.0	0	-	0.3
30	5.0	-	1.8	-	-	-

Scoring system: 0-9 scale, 9 = complete control was somewhat unexpected, as the azoxycyanide moiety was no longer located *ortho* to the ring oxygen. The compound showed excellent prophylactic activity against a number of different diseases of broad-leaf crops (Table 8). In field trials against *Venturia inaequalis* (shown in Table 9), *Plasmopara viticola* and several other diseases, the molecule performed well against heavy infestations. The results from this compound also prompted a further examination of other oxygenated bicyclic systems.

Table 8: Activity of Coumarin-6-azoxycyanide *vs* diseases of broad-leaf crops



Dose (ppm)	*Pv*	*As*
1000	9.0	9.0
300	9.0	9.0
100	9.0	6.9
30	9.0	-

Scoring system: 0-9 scale, 9 = complete control

A 1,3-benzodioxolan-5-azoxycyanide was prepared as part of the development of this part of the project. This compound showed excellent broad spectrum prophylactic activity and, in addition, was one of the first compounds in the series to show any significant levels of therapeutic activity on cereal crops (Table 10). This led, in turn, to an examination of a large number of different ketals, but it was found that any substitution at the 2-position led to a dramatic loss in activity. Some dioxane derivatives were also prepared and shown to possess high levels of biological activity (Table 10). As noted previously, the position of the azoxycyanide moiety *vis-à-vis* the ring oxygens was important in determining biological potency.

Two of these analogues, a benzodioxolan and a benzodioxane, were examined in field trials against a number of commercially important diseases. As shown Table 11, both analogues showed activity (in this example against *P. viticola)* comparable with mancozeb, with the benzodioxolan showing better residual control after twenty-seven days.

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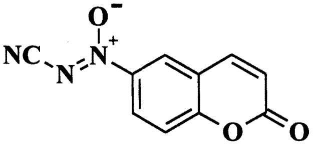
Table 9: Activity of Coumarin Azoxycyanide *vs* *Venturia inaequalis* on Apples in France compared to Captan

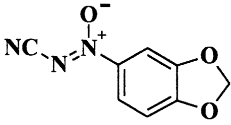


DAT[1]	*Coumarin (500 ppm)*	*Coumarin (1000 ppm)*	*Captan (750 ppm)*	*Captan (1500 ppm)*	*Untreated*
23	2[2]	4	6	6	49
39	2	2	6	8	75
51	0	0	4	1	44
64	1	0	21	10	94

[1] DAT = Days after treatment. After initial treatment, control and test substances applied at 9, 19,24,31,37,44 and 53 DAT

[2] % Disease

Table 10: Activity of benzodioxolan and benzodioxane azoxycyanides *vs* diseases of broad-leaf crops



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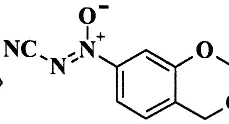

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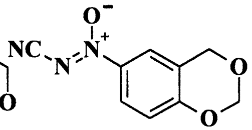

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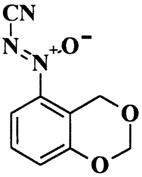

4

	1				*2*		*3*		*4*	
Dose (ppm)	*Pv*	*As*	*Bc*	*Ln*	*As*	*Bc*	*As*	*Bc*	*As*	*Bc*
1000	9.0	9.0	9.0	-	-	-	-	-	-	-
600	-	-	-	-	9.0	9.0	9.0	9.0	7.0	3.0
300	6.7	9.0	9.0	7.0	9.0	8.0	9.0	9.0	-	-
100	6.3	9.0	9.0	2.3	9.0	7.0	9.0	8.7	-	-
30	4.0	-	7.7	1.7	7.0	0.0	1.3	6.7	-	-

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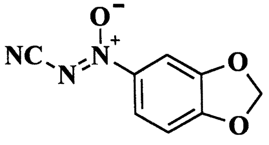
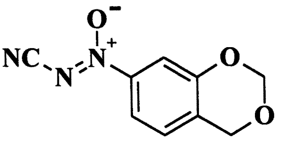
Table 11: Efficacy of benzodioxolan and benzodioxane azoxycyanides compared with mancozeb *vs P. viticola* (Vines, France)



A



B

Mancozeb

C

DAT[1]	*A (500)*[2]	*A (1000)*	*B (500)*	*B (1000)*	*C (700)*	*C (1400)*	*C (2800)*
19	71[3]	98	92	98	98	96	100
27	81	91	59	58	64	71	75

[1] DAT = Days after treatment. [2] Doses in ppm. [3] % Disease control

Conclusion

In the course of this project, over five hundred azoxycyanides were prepared and examined as potential agricultural fungicides. Many of these analogues showed good levels of biological potency, making it difficult to determine clear structure-activity relationships. However four compounds did show significantly greater activity than the others, leading to a field programme designed to evaluate these compounds as potential products. Unfortunately, although the compounds did show activity greater than that of the standards, they did not reach the levels of disease control requisite for commercial development.

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Publication Date: July 29, 2001 | doi: 10.1021/bk-2002-0800.ch028

Chapter 28

The Identification and Optimization of Oömycete Dihydroorotate Dehydrogenase Inhibitors as Fungicides

Marshall H. Parker, Greg L. Durst, Anna C. Hannum, Matthew J. Henry, Lori K. Lawler, and Amy J. Smith

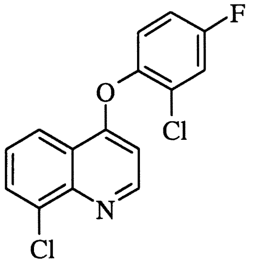
**Dow AgroSciences LLC, 9330 Zionsville Road,
Indianapolis, IN 46268–1053**

The present study describes the discovery of novel antifungal compounds by using a known antifungal target from one class of fungi and exploiting this novel mode of action for the discovery of fungicides in Oömycete plant pathogens. Utilizing computational clustering for compound selection and a novel dihydroorotate dehydrogenase (DHO-DH) enzyme assay, a moderate *in vitro* active (I_{50}= 1.98 μM) was identified. Through both classical structural activity relationship (SAR) investigations and pharmacophore modeling, this new class of aza-chalcones was optimized to provide a series of nM inhibitors of *Pythium aphanidermatum* DHO-DH.

The discovery and validation of novel agrochemically relevant target sites defines the charter of most lead discovery groups across the industry. Accordingly, when a new mode of action (MOA) is discovered and the biochemical target site validated, significant resources supporting multiple approaches are activated to quickly define its potential. One such approach,

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

undertaken within Dow AgroSciences, stemmed from original investigations of dihydroorotate dehydrogenase (DHO-DH), the target site of LY214352 (*1,2*). This inhibitor is highly fungicidal to the Ascomycetous fungi ***Botrytis cinerea*, *Pyricularia oryzae*, *Venturia inaequalis*** and ***Aspergillus nidulans*.** In contrast, LY214352 and related 8-chloroquinoline based inhibitors are not fungicidal to Oömyceteous and Basidiomycetous plant pathogens or bacteria, presumably due to their inactivity at the Oömycete DHO-DH target site. The goal of this effort was to find new lead chemistries that inhibited Oömycete DHO-DH and provided whole plant protection.



LY214352

DHO-DH is an enzyme in the pyrimidine biosynthetic pathway that is responsible for the conversion of dihydroorotate to orotate. Many 8-chloro-4-phenoxyquinolines, including phenoxyquinoline LY214352, demonstrate inhibition of DHO-DH from Ascomycetous fungi such as *P. oryzae* and *A. nidulans*. Moreover, this enzyme inhibition translates to product level *in vivo* control of *B. cinerea*. The specificity of LY214352 was accredited to the assumption that the DHO-DH enzyme was not well conserved between classes of fungi. The implication was that a single compound with this MOA was unlikely to be a broad spectrum fungicide. These factors were the basis for a strategic shift in the DHO-DH target site team to re-align on an Oömycete product concept and focus on a group of taxonomically similar pathogens.

To achieve this goal, several obstacles had to be overcome. First, there were no reported procedures published for the isolation of an Oömycete DHO-DH enzyme and consequently no known inhibitors which were needed to establish a foundation for chemical exploitation of the target site. And finally, there were no high through-put assays in place to directly, indirectly, or virtually screen a representative collection of potential leads to establish that foundation. The following paper details the work associated with identifying and optimizing a new class of DHO-DH inhibitors, the aza-chalcones. This work was critically dependent on the development and implementation of an *in vitro* high through-

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put screen (HTS) against Oömycete DHO-DH, the details of which have been recently patented (3).

Lead Identification

One of the first tasks facing the target site team was defining the collection of chemistries to screen against the newly identified Oömycete DHO-DH target site. Initially, the Oömycete DHO-DH screen was limited to 1,000 compounds a month. A three-month window was defined for the initial screening process, setting a target library size of 3000 compounds. Toward this end, a collection of 15,000 compounds was computationally reduced to 1,500 clusters based on connectivity indices and a non-hierarchical clustering algorithm. Cluster sampling was done in two steps. First, the centroid of each cluster was selected to give 1,500 compounds. Second, a stratified random sampling of larger clusters was conducted. The combined subsets represented 2,970 compounds that were screened against the *P. aphanidermatum* DHO-DH enzyme. This process identified 83 (2.8%) novel actives. Clusters that represented the 83 actives were resampled based on similarity and dissimilarity to the original hit to generate a biased collection of 173 potential inhibitors. Of the 173 compounds selected through this resampling process, an additional 15 (8.7%) novel core structures were identified as active. The actives from both screens were refined through a comparison of *in vitro* (*P. aphanidermatum*) and *in vivo* (*Plasmopara viticola*) activity to rank the final selection of compounds with a bias toward greenhouse activity and a desirable absorption, distribution, metabolism, and "excretion" (ADME) profile. Representative molecules identified in this process are shown in Figure 1. Ultimately, the aza-chalcone series, represented by lead compound **1** (Figure 2), was selected for the synthetic exploitation of this "new" target site.

In vitro Lead Optimization

With lead **1** identified, a similarity search of the Dow AgroSciences database provided 35 additional compounds for testing. Of these 35, the best P. aphanidermatum DHO-DH enzyme inhibitor was chalcone **2** (Figure 2) with an I_{50} value of 0.13 μM. The remaining inhibitors were used to define the scope of the initial SAR around the aza-chalcones. For analog comparison, enzyme inhibition activity has been converted to a relative activity ratio (Relac) to a standard used in each enzyme assay throughout this series (4)

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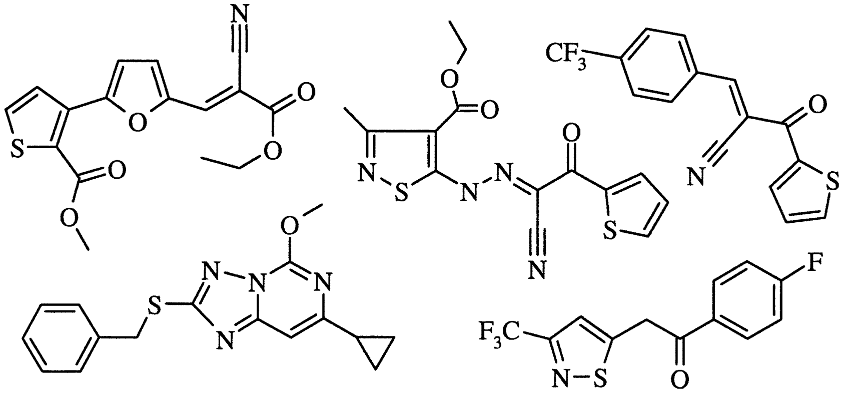
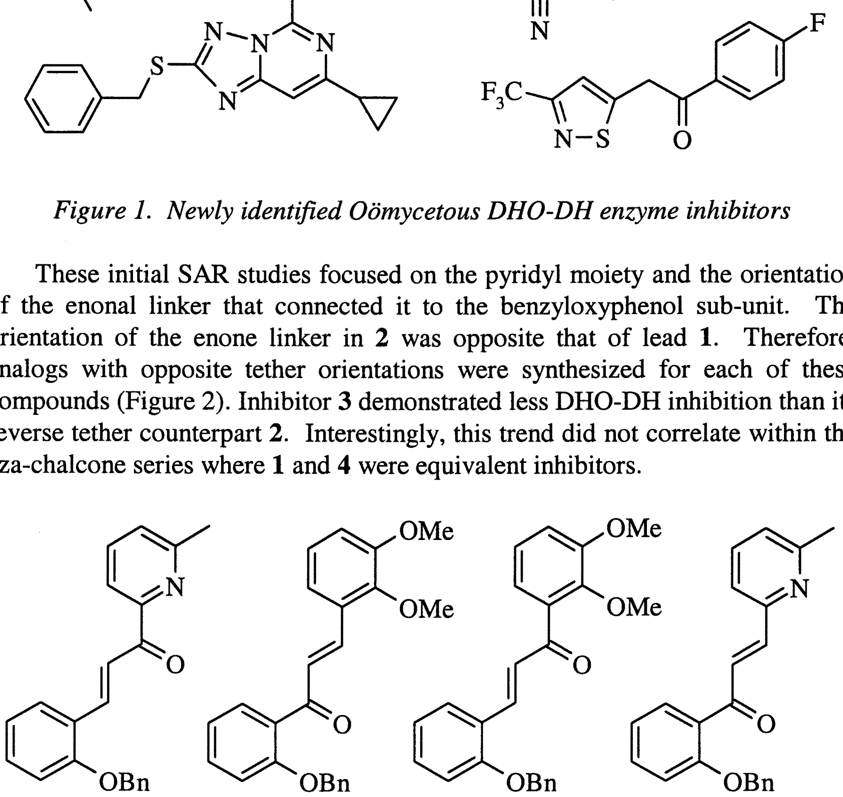


Figure 1. Newly identified Oömycetous DHO-DH enzyme inhibitors

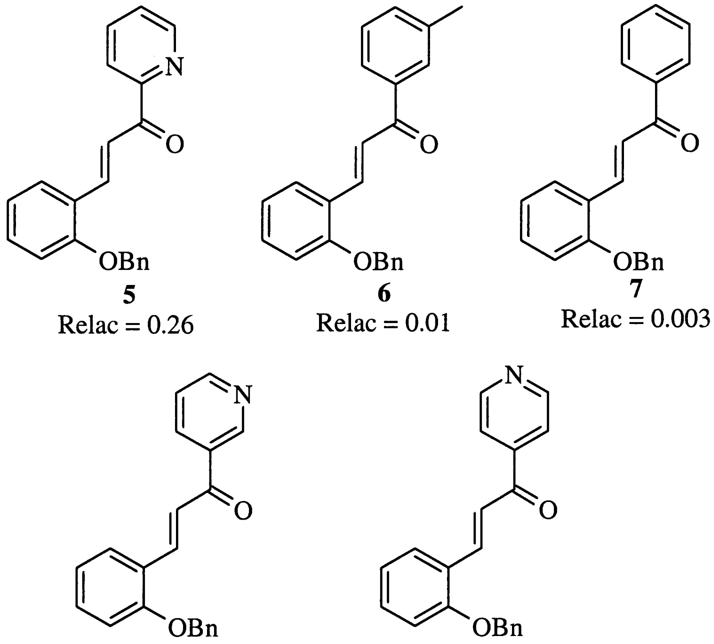
These initial SAR studies focused on the pyridyl moiety and the orientation of the enonal linker that connected it to the benzyloxyphenol sub-unit. The orientation of the enone linker in **2** was opposite that of lead **1**. Therefore, analogs with opposite tether orientations were synthesized for each of these compounds (Figure 2). Inhibitor **3** demonstrated less DHO-DH inhibition than its reverse tether counterpart **2**. Interestingly, this trend did not correlate within the aza-chalcone series where **1** and **4** were equivalent inhibitors.



1 Relac[a] = 0.04
2 Relac = 0.9
3 Relac = 0.007
4 Relac = 0.04

Figure 2. Initial pyridyl moiety in vitro SAR

The necessity of the pyridine ring and its optimal orientation were critical to establish the scope of the chemistry early in this SAR. These questions were addressed with a series of five compounds (Figure 3). This series began with the lead compound **1** and systematically removed both the pyridyl methyl group (**5**) and nitrogen atom (**6**) independently and then simultaneously (**7**). Additional analogs **8** and **9** probed the orientation of the pyridine nitrogen atom. At this point in the SAR, the most active inhibitor was still the dimethoxy-chalcone **2**. However, a comparison of **5**, **6**, and **7** indicated the pyridyl nitrogen was contributing to favorable binding interactions. Additionally, analog **5** demonstrated 90% disease control against *P. viticola* at 400 ppm in a 1 day protectant test. Comparatively, the chalcone analogs **2**, **6**, and **7** were inactive in the same screen.



5
Relac = 0.26

6
Relac = 0.01

7
Relac = 0.003

8
Relac = 0.01

9
Relac <0.0005

Figure 3. SAR of the pyridyl nitrogen

The necessity of the benzyloxy substitution on the central aromatic ring and its positional restrictions was also addressed early in the SAR. The three positional variants of **5**, the meta (**10**), para (**11**), and des (**12**) benzyloxy analogs, were all less active than the parent compound (Figure 4).

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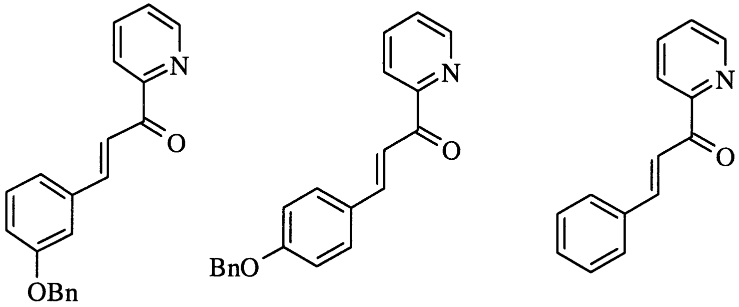


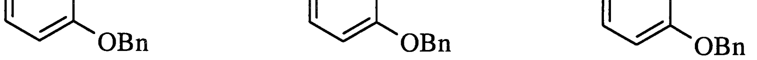
10
Relac = 0.01

11
Relac < 0.0005

12
Relac <0.0005

Figure 4. Initial SAR of the benzyloxy phenol

The composition of the tether linking the pyridine ring with the central phenyl moiety was investigated next. Reduction of the α,β-unsaturated ketone of **5** under various conditions produced the allylic alcohol **13**, saturated ketone **14**, and saturated alcohol **15** (Figure 5). Each of the reduced analogs showed measurable enzyme inhibition but the ketone analog **14** was almost four times more active than the parent enone analog **5**. Additionally, ketone **14** had excellent enzyme activity ($I_{50} = 90$ nM) and favorable solubility properties in the assay medium. Consequently, **14** was used as the internal standard in determining Relac values for this series (*4*).



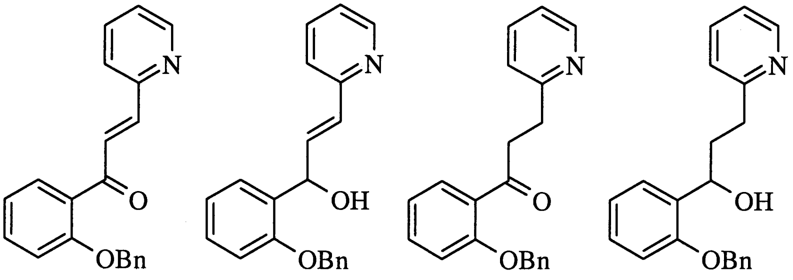
13
Relac = 0.10

14
Relac = 1.00

15
Relac = 0.09

Figure 5. Initial SAR of pyridyl linker

As previously noted, the position of the carbonyl moiety either proximal or distal to the central ring had a dramatic effect on enzyme inhibition in the chalcone series, but relatively none in the aza-chalcone series (Figure 2). To further probe this issue, α,β-unsaturated ketone **16** was synthesized and reduced under various conditions to provide a series of compounds **17-19** (Figure 6) analogous to **13-15**. Allylic alcohol **17** was significantly more active than the saturated ketone **18** and the saturated alcohol **19**, and was two and half times as active as the standard, ketone **14**. For comparison, it is noteworthy that enone **16** and ketone **18** have nearly the same inhibition as the original lead **1**, highlighting the 100 fold increase in enzyme inhibition of **17**, one of the first 25 compounds made in this series.



16 Relac = 0.01
17 Relac = 2.5
18 Relac = 0.02
19 Relac = 0.27

Figure 6. Initial SAR of reverse pyridyl linker

At this point in the SAR, **17** represented the most active *in vitro* analog with almost three-fold better inhibition than the lead compound **1**. Structural analysis showed that the 2-pyridyl and ortho-benzyloxy analogs provided better enzyme inhibition than their structural counterparts and that removal of either the pyridine nitrogen or the benzyloxy group was detrimental to activity. Also, with these components in place, allylic alcohols with the hydrogen bond donor/ acceptor closer to the central ring system were the most active at the target site.

Target Site Validation

The lead compound, **1**, inhibited DHO-DH from *P. aphanidermatum* with an I_{50} value of 1.89 μM, but at 10 μg/mL gave little *in vitro* growth control of the same pathogen. This lack of fungal growth control at reasonable rates by **1** hindered initial efforts to confirm that the pyrimidine biosynthesis pathway was

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being inhibited. Fortunately, the more potent inhibitors of DHO-DH, **14** (I_{50}= 90 nM) and **17** (I_{50}= 50 nM), demonstrated *in vitro* growth inhibition at reasonable rates. This allowed a target site validation experiment that determined that DHO-DH inhibition was in fact responsible for the observed fungal growth inhibition. The results are shown in Table I. *P. aphanidermatum* radial growth was measured in the presence of **14** or **17** at three rates, with and without uridine, and percent inhibition values were calculated based on uninhibited controls. The addition of uridine completely reversed growth inhibition and indicates that inhibition of DHO-DH is responsible for the inhibition of fungal growth.

TABLE I. Uridine growth reversal study

	% Inhibition of *P. aphanidermatum* Radial Growth on Agar			
	ACH-**14**		ACH-**17**	
Rate (μg/mL)	- Uridine	+ Uridine	- Uridine	+ Uridine
10.0	97	0	100	0
1.0	0	0	100	0
0.1	0	0	98	0

Refinement of the Pharmacophore Model

Validation that inhibition of the targeted enzyme represented a lethal event to the host was a key milestone in the project. During the course of this achievement, two collections of inhibitors were identified that represented I_{50} values ranging from 11 to 0.09 μM. With this information a model of enzyme inhibition was constructed with the MSI/Biocad CATALYST™ software. CATALYST™ finds a 3-D arrangement of chemical features, (i.e. H-bond acceptors, donors and lipophillic regions) that best explain the measured inhibition data. Two separate 3-D models were constructed. The first was based on the diverse set of inhibitors identified in the original screening process. The second was based on those compounds related to the ACH substructure. A comparison of the models (Figure 7) highlighted a need to further explore the H-bond donating and accepting capabilities of the pyridyl and benzyloxy tethers to refine the pharmacophore model. Additionally, the ambiguity of this region offered an opportunity to modify overall ADME properties while still maintaining good enzyme inhibition. The remainder of the project addressed these pharmacophore issues with a focus on obtaining improvements in whole plant activity.

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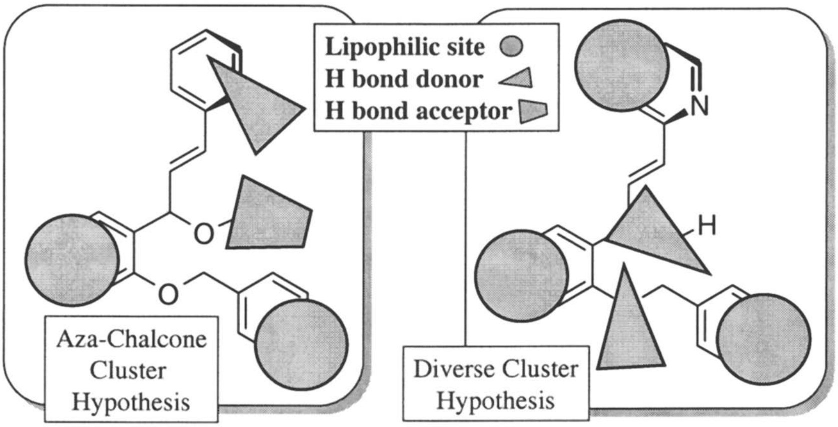

Lipophilic site ●
H bond donor
H bond acceptor
O
O
Aza-Chalcone Cluster Hypothesis
N
H
Diverse Cluster Hypothesis

Figure 7. Pharmacophore Models

The necessity of the hydrogen bonding ability of the allylic alcohol linker of **17** was the first critical question to be investigated. Analogs **20-24** were designed and synthesized (Figure 8) to vary the available hydrogen bond donating and accepting ability. Surprisingly, analogs **22** (I_{50}= 17 nM) and **24** (I_{50}= 9 nM) were better inhibitors of the enzyme than **17,** but contained no hydrogen bonding components in the pyridyl tether. This implied the H-bond donating or accepting ability of the allylic alcohol or similar tether substituents was not critical to enzyme activity. It was then hypothesized that H-bonding may facilitate the ligand-protein interaction with either the allylic alcohol or the benzyl ether and that in compounds **22** and **24**, the benzyl ether was taking a more active role.

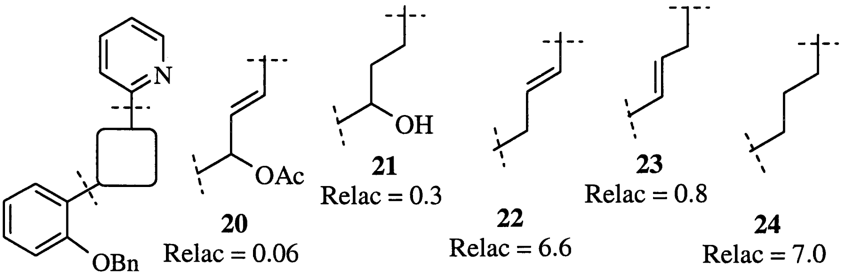
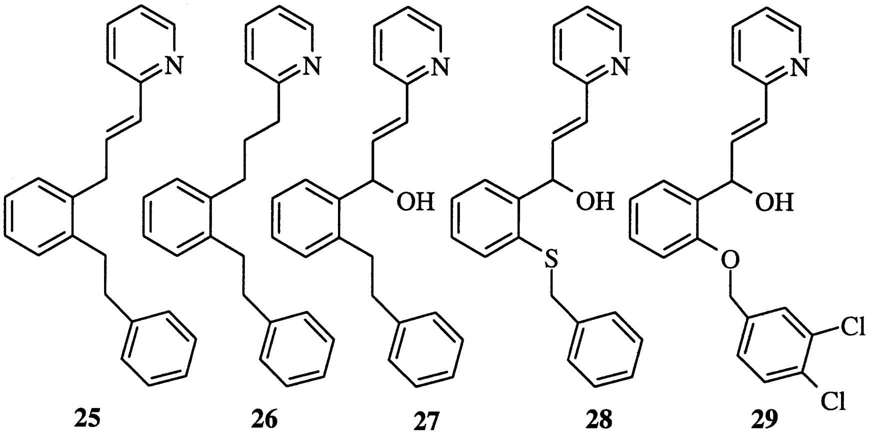

N
OBn
OAc
20
Relac = 0.06
OH
21
Relac = 0.3
22
Relac = 6.6
23
Relac = 0.8
24
Relac = 7.0

Figure 8. Pyridyl tether evaluation

To test this hypothesis, **25** and **26** which removed all the H-donors and acceptors from both tethers were synthethsized and tested (Figure 9). This effort did little to refine the pharmacological model data as these also demonstrated moderate to good enzyme inhibition. Fortunately, evaluation of the whole plant data associated with these compounds provided some additional insight. The des-heteroatom-tethered compounds (**22**-**26**) failed to demonstrate even moderate activity against *P. viticola* at 400 ppm. In contrast, when the pyridyl tether contained an allylic alcohol or related moiety (**20**-**21**, **27**-**29**) the compounds demonstrated >95% disease control against the same pathogen in the greenhouse. This represented an improvement over the <50% disease control demonstrated by lead compound **1** in a similar test. These compounds also represented some of the best enzyme inhibitors: the best being dichloro analog **29** with an I_{50}= 5 nM.



25 Relac = 4.4
26 Relac = 1.3
27 Relac = 3.4
28 Relac = 5.8
29 Relac = 8.5

Figure 9. Benzyloxy tether evaluation

At this point, the project team had identified and optimized a novel *in vitro* lead that demonstrated excellent *in vitro* growth inhibition and some whole plant efficacy. The next challenge was to identify the limiting factor in improving the whole plant activity. One of the leading hypotheses was that the compounds were unstable to UV light. To determine the photostability of the ACH series compounds **14** and **25** were tested for decomposition on both Teflon disks and grape leaves. The compounds were tested at 1 mg/mL in 10% acetone, 0.1% Triton X100 to mimic traditional spraying conditions, at a total application rate of 100 μg per disk or leaf. After the compound applications dried, they were placed in a greenhouse where they received 16 hours of light per day (sunlight and artificial light from metal halide lamps). After 7 days, 25% of **14** and 10% of **25** were still present in or on the grape leaves. In comparison, 100% of the

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dimethomorph standard was recovered. In the Teflon disk studies conducted for the same period of time, only 20% of **14** and none of **25** were recovered. Interestingly, only 50% of the applied dimethomorph was recovered from the Teflon disk study, which implied the compound was being taken into the leaf and protected from the UV light. In the control experiments which were run in the dark on Teflon disks, 95% dimethomorph, 90% **14**, and 85% **25** of the applied material were recovered. It was concluded that both **14** and **25** were photo-unstable and neither possessed the appropriate ADME properties to take advantage of the plants' ability to provide some natural UV protection.

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Conclusion

This work demonstrated a process for the exploitation of a proven MOA against a product concept where the target site was not well conserved between pathogens and has otherwise gone unexplored. A computational clustering analysis was used to refine an internal collection of compounds. These compounds were screened against DHO-DH isolated form *P. aphanidermatum* to identify several novel inhibitors. These results were used to prioritize potential leads and construct a pharmacophore model to guide additional research. The newly identified aza-chalchone series was optimized through traditional and computationally supported SAR studies to deliver new nM inhibitors of DHO-DH from *P. aphanidermatum*. Additionally, improvement in whole plant protection was demonstrated against key Oömycete target *P. viticola*. Finally one hypothesis for the less then optimal translation of *in vitro* to *in vivo* activity in the greenhouse was validated through UV stability studies.

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4. Relative activity is defined as the I_{50} value of the standard (aza-chalcone **14**) in any given assay divided by the I_{50} value of analog of comparison. Relac values were used to standardize data that resulted of variations in the partially purified enzyme activities utilized in these assays.

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Chapter 29

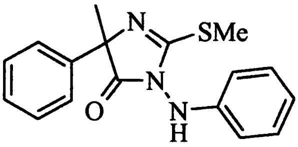
The Synthesis of Novel Imidazolinones as Potential Fungicides

William G. Whittingham, W. Roderick Mound, Sally E. Russell, Brian L. Pilkington†, Anthony M. Kozakiewicz, David J. Hughes, Michael D. Turnbull, and Alan J. Whittle

Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, United Kingdom
†Deceased

A series of imidazolinones bearing oxime ether side chains show good levels of antifungal activity. The methods developed for the synthesis of these materials are described. Some of the key features of the antifungal SAR are briefly discussed with particular reference to the spectrum of activity and potential for systemic redistribution.

In our ongoing search for novel fungicides, we were intrigued by reports from Rhone-Poulenc (*1*) of a series of antifungal imidazolinones, typified by compound **1**.



1

Synthesis and testing of imidazolinone **1** confirmed that it had potent antifungal activity against Oomycete fungi. Of particular interest were the compound's activity when applied as either a foliar spray or a root drench, and

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

the lack of any phytotoxic symptoms. However, the antifungal activity of compound **1** and close analogues was essentially limited to the Oomycete class of fungi, with some weaker activity against rusts.

Biochemical testing demonstrated that **1** was an inhibitor of complex III of the mitochondrial electron transport chain (*2*). From our experience with the strobilurins, we knew that this mode of action had the potential to provide highly potent and broad spectrum fungicidal effects. We therefore embarked on a search for novel imidazolinones which would combine the highly systemic effects of compound **1** with the antifungal spectrum of the strobilurins.

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Oxime Ethers

Drawing on our previous experience in the strobilurin area, we knew that an oxime ether could successfully act as a bioisosteric replacement for a phenyl ring. We therefore selected imidazolinones of structure **6** as our first targets (Figure 1). Disconnection of the oxime revealed the key intermediate, hydroxymethylimidazolinone **4**, which could in turn be prepared from methylimidazolinone **3**.

Chemistry

We first synthesised **3** using the route described in the literature for compound **1** (*1*). However, for our target, **3**, this method proved somewhat unreliable and low yielding. We therefore developed the modified approach outlined in Figure 1. Ring formation was carried out directly from alanine methyl ester by reaction with dithiocarbamate **2** (*3*). *S*-Methylation provided the imidazolinone **3** in 57% overall yield. Hydroxymethylation was achieved in good yield by deprotonation followed by reaction with gaseous formaldehyde. However the requirement for freshly generated gaseous formaldehyde proved operationally difficult on a large scale. A modification of the route that used α-methylserine methyl ester as starting material avoided the necessity for this step and proved efficient for the synthesis of multi-gram quantities of **4**.

With **4** in hand, the hydroxylamine **5** was prepared by Mitsunobu reaction followed by phthalimide cleavage (*4*). Reaction of **5** with a range of ketones and aldehydes under mildly acidic conditions proceeded smoothly to provide the target oxime ethers **6** in good yield.

It proved necessary to carefully control the conditions for phthalimide cleavage and oxime ether formation in order to obtain good yields of the desired products. Changes in reaction pH or solvent resulted in rearrangement of the imidazolinone to form a 6-membered ring **7** as shown in Figure 2.

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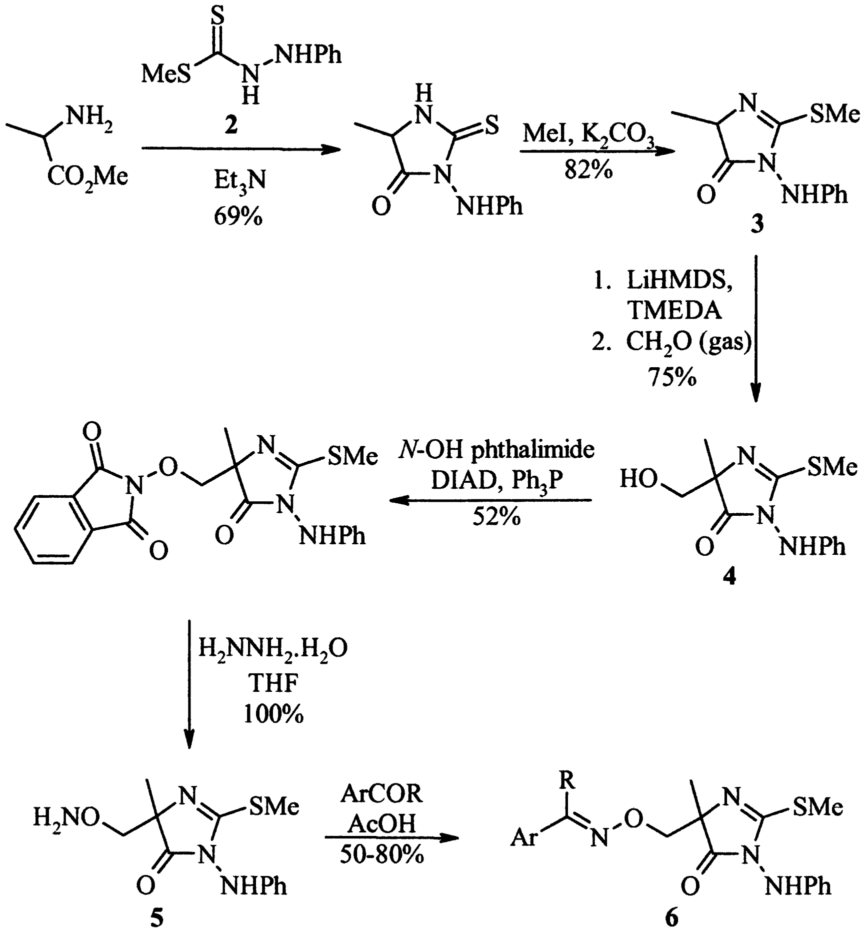

NH2
CO2Me
S
MeS
NHPh
N
H
2
Et3N
69%
H
N
S
O
N
NHPh
MeI, K2CO3
82%
N
SMe
O
N
NHPh
3
1. LiHMDS,
TMEDA
2. CH2O (gas)
75%
HO
4
N-OH phthalimide
DIAD, Ph3P
52%
O
N
O
H2NNH2.H2O
THF
100%
H2NO
5
ArCOR
AcOH
50-80%
R
Ar
N
O
6

Figure 1. Synthesis of Imidazolinone Oxime Ethers

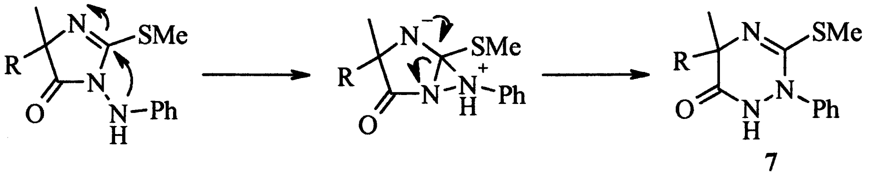
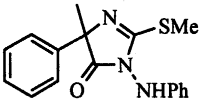
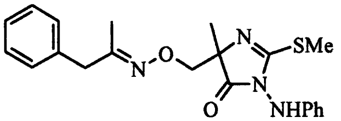
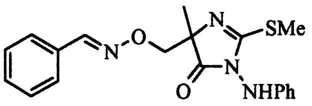
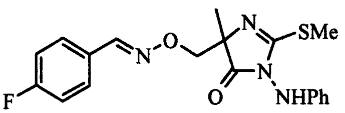
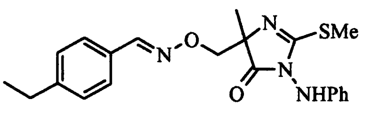

R
N
SMe
O
N
N–Ph
H
+
R
N
SMe
N
Ph
O
N
H
7

Figure 2. Postulated Mechanism for Rearrangement of Imidazolinones

Biological Activity

Testing oxime ethers **6** against beef heart mitochondria demonstrated that some of the compounds had moderate activity as inhibitors of respiration (*2*). The most active were about twenty times weaker than the lead **1** (Table I). In general an aromatic group in the side chain, as in compounds **8-11**, was required for activity.

Table I. Biochemical and Antifungal Activity of Selected Oxime Ethers

Cpd No	*Structure*	*IC_{50}*[a] *(μM)*	*Protectant Breakpoint*[b] *(ppm)*		
			Plasvi[c] *Foliar*	*Plasvi*[c] *Root*	*Puccrt*[c] *Foliar*
1		0.40	2.1	1.1	120
8		7.9	34	>200	>200
9		9.6	15	150	31
10		9.3	8.5	120	37
11		NT	15	>200	27

[a] IC_{50} for inhibition of respiration in beef heart mitochondria. NT = not tested.

[b] IC_{90} for inhibition of fungal growth on whole plants. Compound was applied 1 day before inoculation with fungi. *Foliar* indicates application of compound by foliar spray, *Root* by soil drench.

[c] The following abbreviations are used for fungal diseases: *Plasvi, Plasmopara viticola; Puccrt, Puccinia recondita tritici; Ventin, Venturia inaequalis*

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When applied to plants as a foliar spray the oxime ethers derived from ketones, for example **8**, showed some protectant antifungal activity against Oomycetes. Although of similar activity at the mitochondrial level, aldoxime ethers such as **9-11** showed a broader spectrum of antifungal activity, with better activity against rust (*Puccinia recondita tritici*) than the standard **1**. Compounds **9** and **10** also showed weak systemic activity when applied as a root drench.

Although the activity seen with the oxime ethers was encouraging, we were unable to increase the level of activity above that achieved with the compounds in Table I. We therefore decided to turn our attention to other side chains on the imidazolinone core.

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"Reversed" Oxime Ethers

One possible hypothesis for the weak activity of the oxime ethers was that these compounds had a flexible link between the imidazolinone ring and planar oxime ether group, in contrast to **1** in which the phenyl group is directly linked to the ring. This idea was supported by the lack of activity of other simple derivatives of hydroxymethylimidazolinone **4**.

We reasoned that oxidation of **4** to the aldehyde **12** would provide a versatile intermediate for a variety of side chains with a planar region adjacent to the imidazolinone ring. In view of the activity seen with the oxime ethers, we were particularly interested in the related "reversed" oxime ethers, for example **13** and **14**, which could be derived from aldehyde **12**.

Synthetic Methods

We envisaged that the reversed oxime ethers could be readily prepared by the route outlined in Figure 3. Oxidation of the hydroxymethylimidazolinone **4** was carried out under Swern conditions (*5, 6*) and appeared to proceed smoothly. However, all attempts to purify the aldehyde **12** resulted in isolation of methylimidazolinone **3**. Analysis of the reaction mixture suggested that the aldehyde was formed in good yield, but was breaking down during the isolation procedure, probably due to rapid aerial oxidation followed by decarboxylation of the resulting β-carbonyl acid.

In view of the apparent instability of aldehyde **12**, we decided to try and trap this material without isolation. The oxidation was carried out under standard conditions, then *O*-benzylhydroxylamine added to the reaction mixture. Under these conditions, with the pH of the mixture carefully controlled, we were delighted to obtain a reasonable overall yield of the desired product **13**.

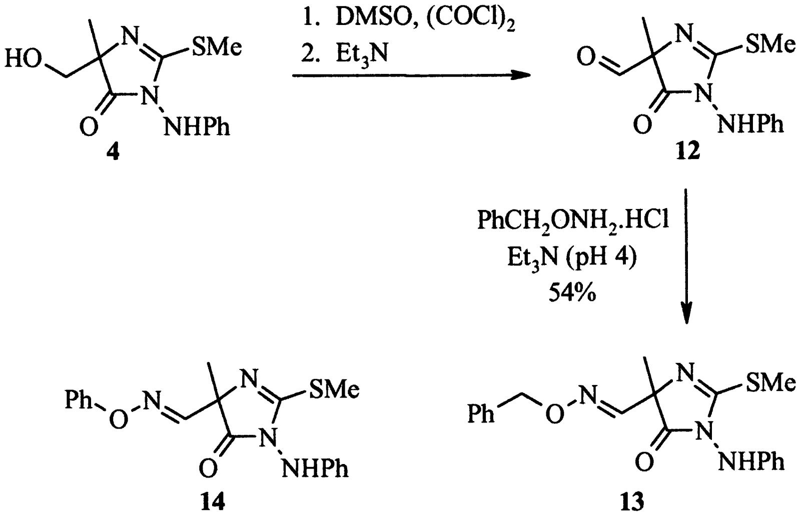
HO
N
SMe
N
O
NHPh
4
1. DMSO, $(COCl)_2$
2. Et_3N
O
N
SMe
N
O
NHPh
12
$PhCH_2ONH_2.HCl$
Et_3N (pH 4)
54%
Ph
O
N
N
SMe
N
O
NHPh
14
Ph
O
N
N
SMe
N
O
NHPh
13

Figure 3. Synthesis of Reversed Oxime Ethers

Using this method, we were able to prepare a range of analogues of phenyl oxime ether **14**, including *O*-heteroaryl systems. A number of these compounds proved to be rather unstable, especially those having an electron-poor aromatic or heteroaromatic ring. Further investigation of the breakdown products showed that decomposition occurred by elimination of phenoxide and formation of the biologically inactive cyano-substituted imidazolinone **15**, as shown in Figure 4.

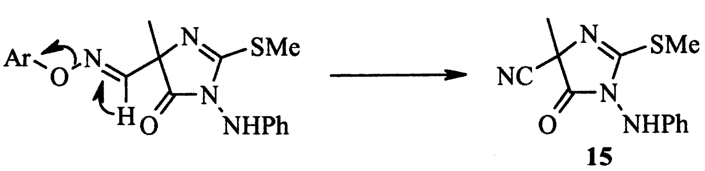
Ar
O
N
H
N
SMe
N
O
NHPh
NC
N
SMe
N
O
NHPh
15

Figure 4. Breakdown of O*-Aryloximes*

In the light of the instability of the *O*-aryloximes, we turned our attention to the *O*-benzyl compounds, typified by **13**, in which the elimination of phenoxide was not possible.

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Although **13** had been prepared using the route outlined in Figure 3, this had a number of drawbacks. Most importantly, the oxidation-trapping sequence proved to be very substrate-sensitive, and required optimisation for each hydroxylamine. We therefore invested significant effort in devising a more efficient route for the synthesis of the *O*-benzyloximes, as shown in Figure 5.

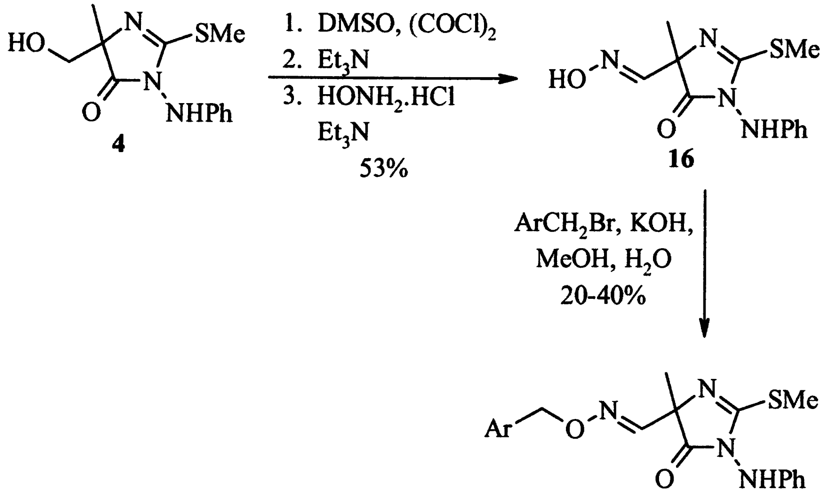

Figure 5. Improved Synthesis of Reversed Oxime Ethers

This route had the advantage that the Swern oxidation-aldehyde trapping sequence could be optimised for hydroxylamine, and this resulted in reliable yields in excess of 50% of the oxime **16**. A further benefit was that **16** proved to be a stable solid that could be purified and stored indefinitely. Many different conditions for *O*-alkylation were investigated. The most reliable conditions were those shown in Figure 5. These gave only modest yields, but were applicable to a wide range of substituted benzyl halides. The route also proved to be readily applied to robotic synthesis, and by this method we were able to rapidly prepare a very wide range of analogues of **13** for structure-activity studies.

We also used this route to prepare a series of heteroaromatic analogues of **13**. These were designed to have a range of physical properties, including those required to demonstrate systemic activity. For these compounds the *O*-alkylation reaction proved to be rather variable and gave very poor yields in some cases.

Similar chemistry was also developed to prepare ketoxime ethers, as shown in Figure 6. Methylimidazolinone **3** was again used as the starting material, and

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could be readily converted into ketone **17**. As expected, this proved to be more stable than aldehyde **12**, and could be isolated and purified. This material could then be converted to oxime ethers **19** and **20**, either directly or *via* oxime **18**.

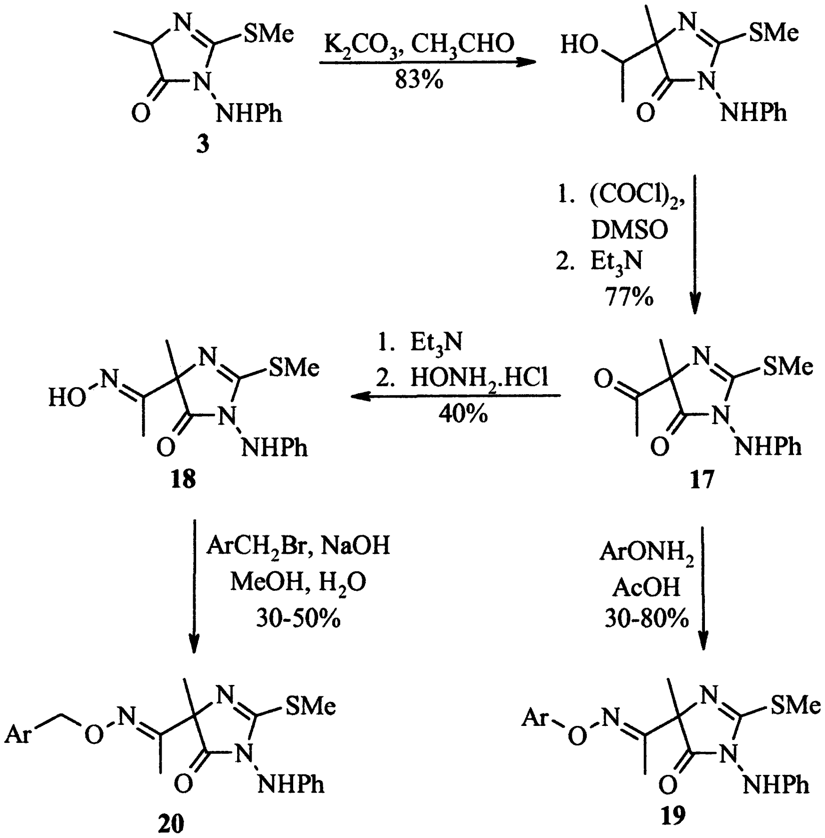
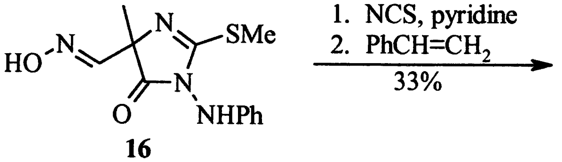
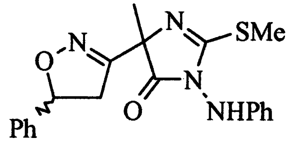

SMe
NHPh
3
K_2CO_3, CH_3CHO
83%
HO
SMe
NHPh
1. $(COCl)_2$, DMSO
2. Et_3N
77%
1. Et_3N
2. $HONH_2.HCl$
40%
HO
SMe
NHPh
18
SMe
NHPh
17
$ArCH_2Br$, NaOH
MeOH, H_2O
30-50%
$ArONH_2$
AcOH
30-80%
Ar
SMe
NHPh
20
Ar
SMe
NHPh
19

Figure 6. Synthesis of Ketoxime Ethers

A series of isoxazolines, for example **21**, were also prepared, as cyclic analogues of the ketoxime ethers. The synthesis of these compounds proved straightforward, as shown in Figure 7. Conversion of oxime **16** to the corresponding nitrile oxide followed by *in situ* trapping with styrene provided the isoxazoline **21** as a mixture of diastereomers.



16



21

Figure 7. Synthesis of Isoxazolines

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Biological Activity

Biological data for a representative selection of the reversed oxime ethers is given in Table II.

One of the first reversed oximes that we made, *O*-phenyloxime **14**, provided us with great encouragement to continue work in this area. Compound **14** was about ten times more active as an inhibitor of respiration than the oxime ethers (see Table I), and only a factor of two weaker than the standard **1**. It showed good levels of foliar protectant activity against Oomycetes, combined with a significantly broader spectrum of fungicide activity than **1**, as demonstrated by activity against rust (*Puccinia recondita tritici*) and apple scab (*Venturia inaequalis*) shown in Table II.

Stability, as discussed above, limited the range of analogues that we were able to make, and none improved on the activity of **14**. This was particularly the case for heterocyclic analogues, for example **22**, which were made in an attempt to improve the systemic properties of the compounds. Blocking the decomposition pathway of these compounds by making ketoximes **19**, typified by compound **23**, restored the potency of protectant activity against Oomycetes, but gave no additional spectrum and weaker inhibition of respiration.

O-Benzyloxime **13** showed similar levels of respiration inhibition and Oomycete activity to **14**, but lacked the broader antifungal spectrum. However, optimisation of this structure, using the new synthetic route outlined in Figure 5, provided compounds that were much more active. The potency of the best compounds as respiration inhibitors was significantly increased; for example, compound **25** had twice the potency of the standard **1**. The best compounds, for example **24**, also showed good potency and spectrum of antifungal effect. However, as expected from their physical properties, these compounds showed no evidence of movement in the plant.

In an effort to improve the systemic activity of the compounds, a number of heterocyclic analogues of **13** were prepared. We hoped that by replacing the

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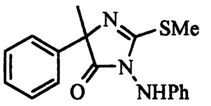
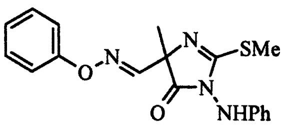
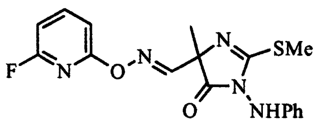
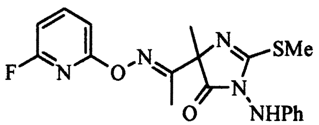
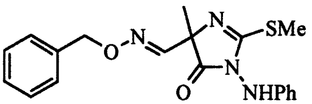
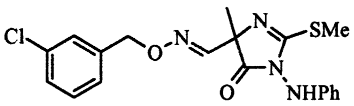
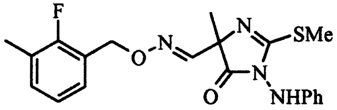
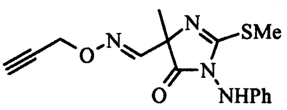
Table II. Biochemical and Antifungal Activity of the "Reversed" Oxime Ethers[a]

Cpd No	*Structure*	*IC$_{50}$ (μM)*	*Protectant Breakpoint (ppm)*			
			Plasvi Foliar	*Plasvi Root*	*Puccrt Foliar*	*Ventin Foliar*
1	 N SMe N O NHPh	0.40	2.1	1.1	120	>200
14	 O N N SMe N O NHPh	0.85	9.7	>200	18	97
22	 F N O N N SMe N O NHPh	5.6	52	>200	150	>200
23	 F N O N N SMe N O NHPh	13	9.4	>200	>200	>200
13	 O N N SMe N O NHPh	0.93	10	>200	129	>200
24	 Cl O N N SMe N O NHPh	0.61	13	>200	8.9	41
25	 F O N N SMe N O NHPh	0.21	23	>200	4.6	>200
26	 O N N SMe N O NHPh	2.0	25	15	>200	>200

[a] For definitions of the terms used, see footnotes to Table I.

benzyl group in **13** with more polar heterocyclylmethyl groups, we could lower the logP (octanol-water) (*7*) to a level where the compounds would move systemically in the plant. If the level of antifungal activity achieved with compounds like **24** could be combined with the systemic movement of **1** we would be close to our goal.

Key biological and physical property data for a representative selection of these compounds are summarised in Table III.

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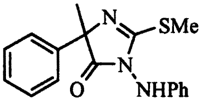
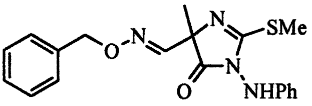
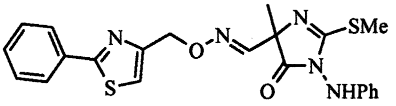
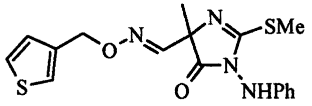
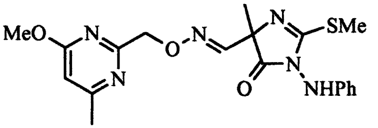
Table III. Foliar and Systemic Activity of Heterocyclic Oxime Ethers

Cpd No	*Structure*	*logP*[a]	*IC$_{50}$*[b] *(μM)*	*% Control Plasvi*[c]	
				Foliar	*Root*
1		3.2	0.40	100	100
13		3.6	0.93	95	0
27		4.0	0.59	95	0
28		3.2	0.68	100	0
29		2.1	>48	4	0

[a] LogP measured (*8*) for compounds **1** and **13**, calculated using the clogP programme (*9*) with a series specific correction for **27-29**.

[b] IC$_{50}$ for inhibition of respiration in beef heart mitochondria.

[c] The percentage control achieved with 30 ppm of the test compound. Other test details are as given in Table I, footnote *b*.

Compound **27**, which was more lipophilic than **13**, showed similar antifungal activity with slightly improved respiration inhibition. Reducing the logP to the same value as **1**, with compound **28**, maintained the activity, but again provided no evidence of systemic movement. Much to our disappointment, more polar compounds, for example **29**, proved to have no activity either as respiration inhibitors or as fungicides. It appears from these results that the level of polarity required in the oxime side chain to achieve the correct physical properties for systemic movement is not tolerated by the active site of the protein.

The only oxime ethers that showed significant systemic activity were those with alkyl side chains such as **26** (Table II). These were equally active against Oomycetes when applied as either a foliar spray or root drench. However, they lacked the potency of the lead compounds and had only a limited spectrum of activity.

The ketoxime ethers **19** and **20** generally had similar activity to the corresponding aldoxime ethers, and did not provide any clear advantage. Isoxazolines such as **21** had very weak activity suggesting that, as would be expected, the oxime ethers adopt an extended conformation at their binding site.

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Conclusions

A number of novel imidazolinones bearing oxime ether side chains show excellent activity as inhibitors of mitochondrial respiration. The best of the compounds show broad spectrum antifungal activity when applied as foliar sprays. However, it was not possible in this series to achieve the high level of systemic antifungal activity that was our target.

Acknowledgments

We would like to thank our many colleagues, in chemistry and other disciplines, at Jealott's Hill who contributed to this work.

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Chapter 30

Synthesis of Fungicidal Triazolones

Richard J. Brown, Barry Ashworth, Joseph E. Drumm[1], Deborah A. Frazier[2], Mary Ann Hanagan, Constance Happersett[3], G. E. Koether[4], D. J. Robinson, King-Mo Sun, and Paul Wojtkowski[5]

**Stine-Haskell Research Center, DuPont Crop Protection,
Newark, DE 19714
[1]Current address: 21 Anglin Drive, Newark, DE 19713
[2]Current address: 2371 Pinnacle Drive, Martinez, CA 94553
[3]Current address: 114 Steven Lane, Wilmington, DE 19808
[4]Current address: 2304 Porter Road, Bear, DE 19701
[5]Current address: 144 Belmont Drive, Wilmington, DE 19808**

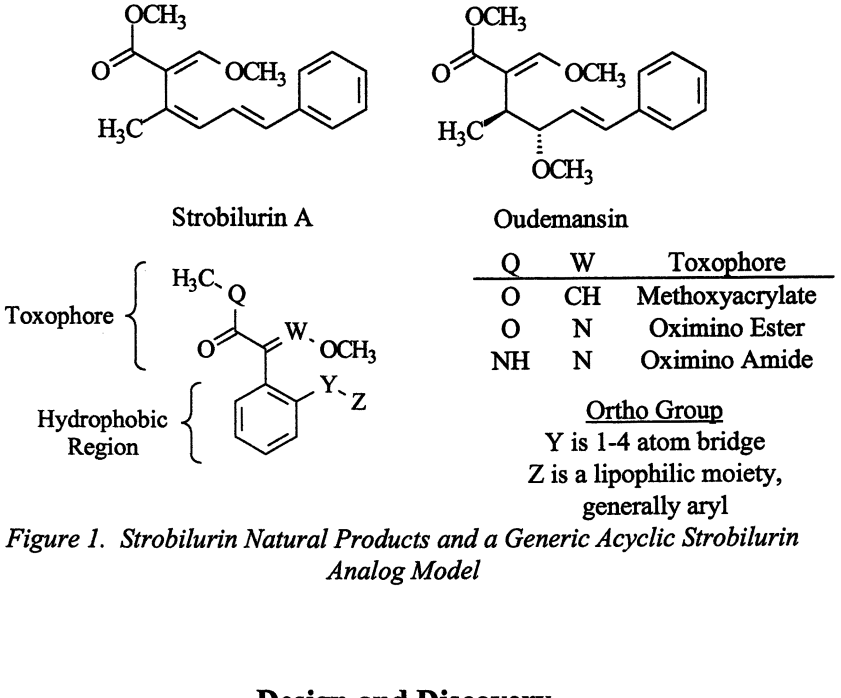
Strobilurin Analogs with cyclic triazolone structures were investigated as potential agricultural fungicides. Aspects of their design and optimization are presented. Biological test data in enzyme and whole organism disease control assays are reported for key analogs. A qualitative assessment of the field performance of some analogs is also provided.

For some time, we have been investigating triazolones as agricultural fungicides (*1*). The evolution of these compounds can be traced to the natural products Strobilurin A and Oudemansin (see Figure 1) isolated from Basidiomycete fungi such as *Strobilurus Tenacellus.* These natural products inhibit mitochondrial respiration by blocking electron transport of the cytochrome bc_1 complex where they bind at the ubihydroquinone:cytochrome-c oxidoreductase site (*2*). The key features of these molecules include a β-methoxyacrylate linked to a hydrophobic tail at the α-position.

Using these natural products as a starting point a number of companies investigated related structures as agricultural fungicides. At the time we began

In Synthesis and Chemistry of Agrochemicals VI; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

our work, the commercial fungicides azoxystrobin (*3*) and kresoxim methyl (*4*) were in development. These synthetic Strobilurin Analogs can be generalized into a generic structure in which a heteroatom-rich "toxophore" with a defined spatial arrangement is bonded to a hydrophobic region consisting of a phenyl ring with a lipophilic group *ortho* to the toxophore (Y-Z). The steric interaction between the toxophore and the group *ortho* to it imparts a twist in the molecule about the phenyl-toxophore axis, in which the toxophore is out of plane in relation to the phenyl ring. This twist appears to be necessary for the observed biological activity, since structures without an *ortho* group are inactive (*2*). Investigations had also suggested that fungicidal activity is conserved by very limited variation of the toxophore, while the lipophilic region could be quite variable and still retain fungicidal activity. Thus, the majority of work in this area, as evidenced by the number of patents, had concentrated on maintaining the toxophore structure and varying the hydrophobic region. There were very few examples in which the toxophore was varied from this model.



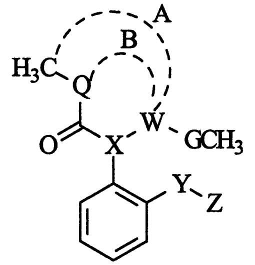
Q	W	Toxophore
O	CH	Methoxyacrylate
O	N	Oximino Ester
NH	N	Oximino Amide

Ortho Group
Y is 1-4 atom bridge
Z is a lipophilic moiety, generally aryl

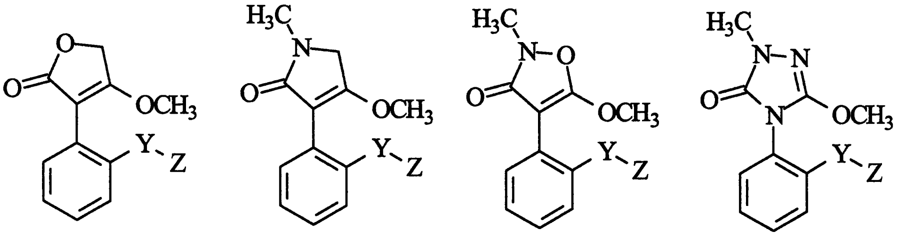
Figure 1. Strobilurin Natural Products and a Generic Acyclic Strobilurin Analog Model

Design and Discovery

Work at DuPont concentrated on investigating cyclic structures as possible toxophores. (see Figure 2). Tying together the toxophore according to path A led to lactones that proved to be inactive as fungicides. Tying together the toxophore with a carbon link according to path B, which allows retention of the methyl group of the acyclic toxophores, led to lactams. These lactams also did not exhibit fungicidal activity in assays. Then, using an oxygen atom as the cyclization link A, we prepared isoxazolones. These structures were found to be active as fungicides, but will not be discussed further here. Changing the connection between the phenyl ring and the toxophore (X) and the cyclization link (B) to nitrogens led to the triazolone toxophore, which also proved to be fungicidal.



G is O or S
Q is O or N
W is =C or -N
X is C or N?
Y is 1-4 atom bridge
Z is a lipophilic moiety, generally aryl



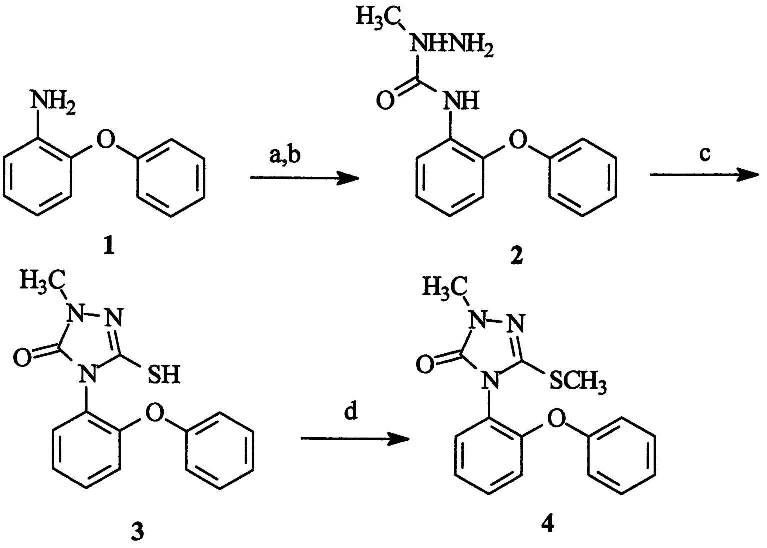
Lactone Lactam Isoxazolone Triazolone

Figure 2. Cyclic Strobilurin Analog Design

Triazolone Synthesis

Our first synthesis of a compound with a triazolone toxophore is shown in Figure 3. Preparation of the semicarbazide **2** was followed by cyclization using thiophosgene. Methylation of compound **3** under basic conditions occurred exclusively on sulfur to provide compound **4**.

Observation of respiration inhibition and fungicidal activity in greenhouse assays for compound **4** (shown in Table I) suggested that we had successfully designed a Strobilurin analog with a cyclic toxophore. Compounds with a hydrogen or small group *ortho* to the toxophore did not exhibit any fungicidal activity, demonstrating the importance of a large *ortho* group in imparting fungicidal activity.



a triphosgene, ethyl acetate, b CH_3NHNH_2, ethyl acetate,
c ClC(=S)Cl, triethylamine, THF, d CH_3I, NaH, THF

Figure 3. Synthesis of First Triazolone Strobilurin Analog

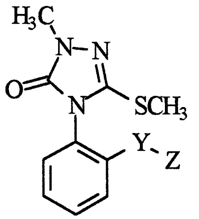
Biological Testing

As an indicator of the intrinsic biological activity of the analogs, we assayed the mitochondrial electron transport, or respiration, of a cell-free preparation of mitochondria isolated from rat hearts. The concentration of compound in solution, measured in parts per billion (ppb), necessary to inhibit respiration to 50% of the native level was determined (IC_{50}) using standard protocols (*5*). In our basic assay, mammalian mitochondria were used for ease of preparation, although mitochondria isolated from fungal organisms provided similar results. We found that this assay generally correlated adequately with whole-organism data to provide a rapid indicator of the fungicidal activity that might be expected. Disease control was determined using the pathogen-host complex grown in greenhouse or growth chambers (*6,7*). Test compounds were applied at rates ranging from 0.4 to 200 parts per million (ppm) and an assessment of the prevention of disease was made by visually scoring the diseased area of the foliage. The raw data, averaged over multiple tests if available, were converted to an estimated dose effective at controlling 90% of the disease (ED_{90}) relative to untreated checks. The diseases assayed included: *Erysiphe graminis f. sp. tritici*, the causal agent of wheat powdery mildew (WPM); *Puccinia recondita*, the causal agent of wheat leaf rust (WLR); *Pseudocercosporella herpotrichoides*, the causal agent of wheat foot rot (WFR); *Septoria nodorum*, the causal agent of wheat glume blotch (WGB); *Phytophthora infestans*, the causal agent of potato and tomato late blight (PLB) and *Plasmopara viticola*, the causal agent of grape downy mildew (GDM).

Other abbreviations for Tables I-IV:

I	Substance Inactive at Rates Tested
NT	Substance Not Tested
A	Substance Active, But an ED_{90} Was Not Calculated

Table I. Assay Performance of First Triazolone Analogs

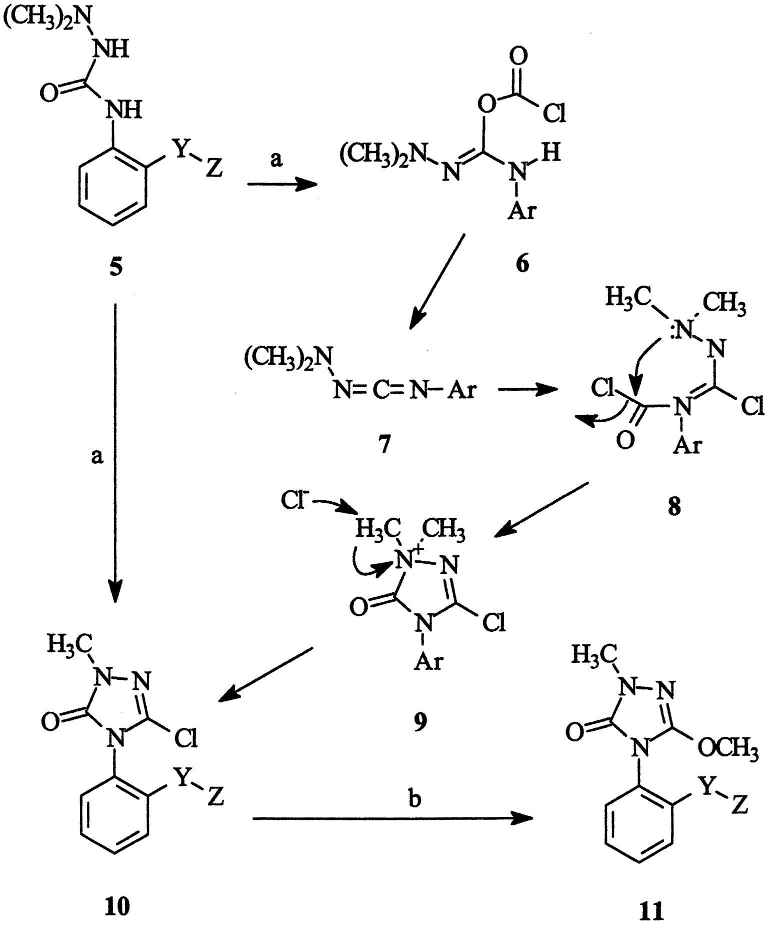


Y-Z	*Resp. Assay IC_{50}, ppb*	*Greenhouse Assays: ED_{90}, ppm*					
		WPM	*WLR*	*WFR*	*WGB*	*PLB*	*GDM*
H	I	I	I	NT	NT	NT	I
OCH_3	I	I	I	NT	NT	NT	I
OPh	2800	190	135	I	380	750	135

Methoxy-substituted Triazolone Synthesis

A general synthesis of the methoxy-substituted triazolone is shown in Figure 4. Heating of the semicarbazide **5** with excess phosgene leads to the chlorotriazolone **10**. The mechanism of this interesting transformation (*8*) involves a dehydration of the semicarbazide **5** by an equivalent of phosgene to provide a carbodiimide-like structure 6. A second equivalent of phosgene adds across the carbodiimide, followed by cyclization to provide the intermediate **9**.

Finally, a von Braun cleavage leads to the chlorotriazolone **10**. Compounds similar to **10** were reported to be resistant to chloride displacement (*8*). However, we found that treatment of **10** with excess sodium methoxide under forcing conditions provided high-yielding methoxide displacement to complete the synthesis of compound **11**.

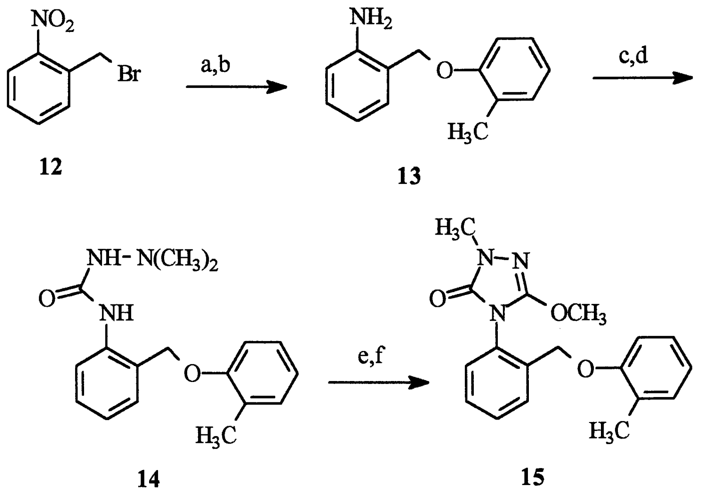


a excess phosgene, ethyl acetate, heat, b 30% $NaOCH_3$, methanol, reflux.

Figure 4. General Synthesis of Methoxytriazolone Strobilurin Analogs

Optimization

With these results we had accomplished our first goals: (1) we had designed novel cyclic toxophores that demonstrated fungicidal activity with a mode of action that matched that of other Strobilurin analogs and (2) we had developed general synthetic methods to prepare them. It remained to be seen if we could find analogs with the triazolone toxophore that would be as active as the acyclic toxophores. Therefore, we began an optimization program to improve upon the activity demonstrated by the first examples of the triazolone toxophores. We began by investigating *ortho* groups that had been found to be particularly good with the acyclic toxophores. One such group is the 2-methylphenoxymethylene group present in the commercial product kresoxim-methyl (*4*). It should be noted that the analog with a 2-methyl group provides better fungicidal activity than the analog without a methyl group. Preparation of a triazolone incorporating this group, compound **15**, is shown in Figure 5. This synthesis makes use of variations of the previously described general synthesis.

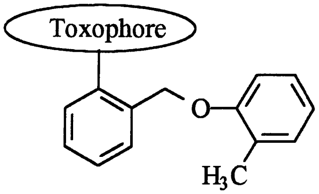


a 2-cresol, K_2CO_3, DMF, b H_2, Pd/C, c triphosgene, ethyl acetate,
d $(CH_3)_2NNH_2$, ethyl acetate, e excess triphosgene, THF, heat,
f 30% $NaOCH_3$, methanol, reflux

Figure 5. Synthesis of the Triazolone Strobilurin Analog with a 2-Methylphenoxymethylene Ortho Group

Comparison of the triazolone toxophore to the acyclic oximino ester toxophore with the 2-methylphenoxymethylene group is shown in Table II. It can be seen that with this group, significant improvement in fungicidal activity was made for the cyclic toxophore over the earlier analog 4. However, it can also be seen that the acyclic toxophore exhibits superior activity with this group.

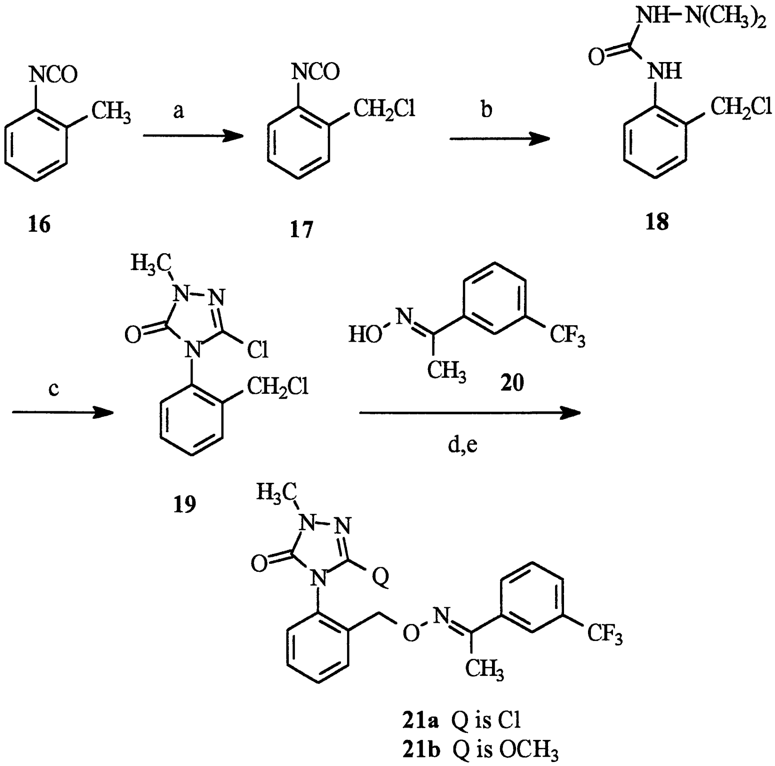
Table II. Toxophore Comparison with the 2-Methylphenoxymethylene Group



Toxophore	*Resp. Assay IC_{50}, ppb*	*Greenhouse Assays: ED_{90}, ppm*					
		WPM	*WLR*	*WFR*	*WGB*	*PLB*	*GDM*
Oximino Ester (Kresoxim Methyl)	64	7	21	135	56	149	8
Triazolone	1000	A	34	I	135	I	A

We also examined aromatic oximes as *ortho* groups. These groups have longer bridges, extending the lipophilic group farther away from the toxophore. A synthesis of a triazolone with an oxime *ortho* group, **21b**, optimized in our Process Development organization is shown in Figure 6. Selective mono-chlorination of the isocyanate **16** was achieved by stopping at 50% conversion and fractional distillation of the mixture of product and starting material. Reaction of the isocyanate **17** with dimethyl hydrazine proceeded with no involvement of the benzyl chloride. Cyclization of **18** to the chlorotriazolone **19** is best carried out by metered addition of **18** to a hot solution of phosgene, maintaining a large excess of phosgene relative to substrate to minimize side reactions. This synthesis can be conducted at multi-kilogram scale to produce the intermediate **19**, which was key to a large number of analog preparations. Reaction with the oxime **20** proceeded exclusively to displace the benzyl chloride, followed by methoxide displacement of the heterocyclic chloride. This two-step sequence could be run either by isolating the intermediate **21a** or in a "single pot" with no loss in yield.

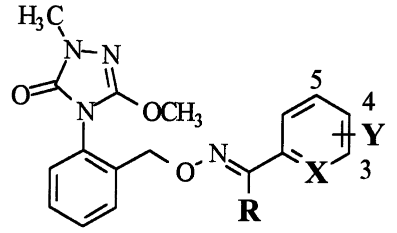
A comparison of the biological activity for a series of triazolones substituted with oximes varied at the position indicated by R is shown in Table III. The substituent R occupies the same space occupied by the methyl group of the 2-methylphenoxymethylene group. A methyl group at that position provided the best overall activity, with ethyl and cyclopropyl groups also providing good activity. The biological activity for a series of triazolones substituted with oximes varied at the positions indicated by X and Y is also shown in Table III. We found that hydrophobic, electron-withdrawing groups at positions *meta* to the oxime bridge provided the best fungicidal activity. A pyridinyl oxime with a CF_3 group *meta* to the oxime was also very active.


NCO
CH3
a
16
NCO
CH2Cl
17
b
NH-N(CH3)2
O
NH
CH2Cl
18
c
H3C
N-N
O
N
Cl
CH2Cl
19
HO
N
CF3
CH3
20
d,e
H3C
N-N
O
N
Q
O
N
CF3
CH3
21a Q is Cl
21b Q is OCH3

a 0.5 equivalents Cl_2, neat, 95% at 48% conversion,
b $H_2NN(CH_3)_2$, ethyl acetate, 98%, c excess phosgene, ethyl acetate, 96%,
d 20, NaH, THF, 92% or KOH, THF, 86%, e $NaOCH_3$, methanol, THF, 95%,
d,e in single pot, 85-91%.

Figure 6. Optimized Synthesis of Triazolone Strobilurin Analogs with an Oxime Ortho Group

Table III. Assay Performance of Triazolone Oximes

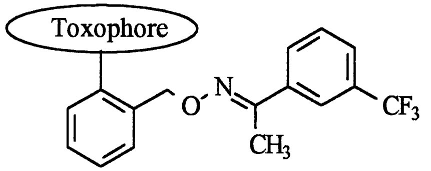


X is CH R	Y	Resp. Assay IC_{50}, ppb	Greenhouse Assays: ED_{90}, ppm WPM	WLR	WFR	WGB	PLB	GDM
H	3,5-$(CF_3)_2$	300	9	I	I	34	NT	A
CH_3	3-CF_3	43	0.9	1	20	16	79	9
C_2H_5	3-CF_3	30	9	9	67	1	NT	9
Cyclo-propyl	4-Cl	148	<2	9	34	9	NT	9
CF_3	3-CF_3	560	34	I	A	I	NT	A
CN	3-CF_3	NT	9	9	67	34	NT	9
OCH_3	3-CF_3	30	1	9	135	34	NT	34
SCH_3	3-CF_3	160	17	17	I	I	NT	34
R is CH_3 X	Y							
CH	4-CF_3	38	1	2	17	50	190	22
CH	3-$Si(CH_3)_3$	2.5	1	0.6	1	1.7	A	18
CH	3,4-Cl_2	17	34	1.7	34	13	67	9
CH	3,5-Cl_2	12	0.6	1	9	1	135	9
CH	3,5-$(CF_3)_2$	14	0.6	7	26	9	A	30
N	5-CF_3	74	1	1	67	9	A	9

A comparison of the biological activity for acyclic and the triazolone toxophores substituted with the 3-trifluoromethylphenyl oxime is shown in Table IV. The compound with the oximino ester toxophore has been subsequently commercialized as trifloxystrobin. One can observe that with this oxime group, the triazolone cyclic toxophore is very competitive with the acyclic toxophores.

The structure-activity relationships of compounds with the triazolone toxophore suggest that the triazolone is inherently not as active as the acyclic toxophores with certain *ortho* groups, although good *ortho* groups with the acyclic toxophores are also good with the triazolone toxophore. These results suggest that given the proper substitution, the cyclic triazolone toxophore can provide fungicidal activity comparable to that of the acyclic toxophores.

Table IV. Toxophore Comparison with an Oxime Group



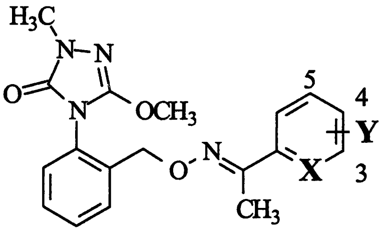
Toxophore	Resp. Assay IC_{50}, ppb	Greenhouse Assays: ED_{90}, ppm					
		WPM	WLR	WFR	WGB	PLB	GDM
Methoxyacrylate	2.8	<2	1	9	A	A	A
Oximino Ester	8.3	0.8	0.6	135	5	67	12
Oximino Amide	30	1	<2	9	A	67	1
Triazolone	43	0.9	1	20	16	79	9

Encouraged by the fungicidal activity observed in the greenhouse with the oxime *ortho* groups, we conducted field trials with several triazolone compounds with varied oxime substituents. The compound substituted with the 3,5-dichlorophenyl oxime was selected for field trials even before we had the results from greenhouse assays. Table V summarizes the field performance for these analogs (*9*). They provided good to excellent control of economically significant diseases for wheat, grape and apple crops. Other diseases were also controlled or suppressed, including barley Rhynchosporium and Helminthosporium, grape Botrytis, potato late blight and rice blast.

Conclusions

We successfully designed and synthesized compounds with novel cyclic toxophores as Strobilurin analogs. The biochemical mode of action is the same as that identified for the previously known acyclic toxophores. The structure-activity relationships for the *ortho* group of the hydrophobic region are roughly parallel between the acyclic and cyclic toxophores. In particular, triazolones with oxime *ortho* groups were obtained in practical, large-scale syntheses and provided commercial levels of disease control in field trials.

Table V. Field Performance for Triazolone Oximes



Disease	*G/Ha*	X is CH Y is 3-CF_3	X is CH Y is 3,5-Cl_2	X is CH Y is 3,5-$(CF_3)_2$	X is N Y is 5-CF_3
Wheat Powdery Mildew	250	++	+++	+++	+++
	125	+	+++	+++	+++
	63	+	NT	+++	++
Wheat Septoria Tritici	250	+++	+++	++	+++
	125	++	+++	++	+++
	63	+	NT	+	NT
Wheat Septoria Nodorum	250	+++	+++	++	+++
	125	++	++	++	++
Wheat Brown Rust	250	++	++	++	NT
	125	++	++	++	NT
	63	+	NT	+	NT
Grape Downy Midew	250	++	+++	+	++
	125	+	++	-	+
	63		NT	NT	-
Grape Powdery Mildew	250	+++	+++	+++(+)	+++
	125	++(+)	+++	++(+)	+++
	63	++	++*	+	++
Grape Black Rot	250	+++	+++	+++	+++
	125	+++	+++	+++	+++
	63	NT	NT	NT	NT
Apple Scab	250	+++	+++	+++	+++
	125	+++	+++	+++	+++
	63	+++	+++*	+++	+++

+++ Competitive Advantage ++ Commercial Levels of Control
+ Suppression of Disease - Ineffective at Rate Tested
* Tested at 50 g/Ha

Acknowledgments

The authors wish to thank all those who made significant contributions to this project, especially our co-workers involved in the synthesis, characterization, biological testing, formulation, soil property evaluations, mode of action studies and toxicology of these compounds.

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